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Irwin & Rippe's Intensive Care Medicine

SEVENTH EDITION

Richard S. Irwin
James M. Rippe

Wolters Kluwer Health | Lippincott Williams & Wilkins

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Irwin and Rippe's INTENSIVE CARE MEDICINE

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PREFACE

It is with great pleasure that we present the seventh edition of *Irwin and Rippe's Intensive Care Medicine*. As with previous editions, the editorial challenge that we faced with the seventh edition was to continue to ensure that the textbook evolved as the field has evolved and improved to meet the varied and rigorous demands placed on it by the diverse group of specialty physicians and nonphysicians practicing in the adult intensive care environment without losing strengths that have made previous editions so useful and popular. We hope and believe that the seventh edition of *Irwin and Rippe's Intensive Care Medicine* has risen to meet these challenges.

Over the past 27 years since the publication of the first edition of our textbook, dramatic changes have occurred in virtually every area of critical care, and these are reflected in the evolution of our textbook. While our textbook initially focused primarily on medical intensive care, it now provides an interdisciplinary emphasis on anesthesia, surgery, trauma, and neurointensive care as well as medical intensive care with strong collaboration across all these disciplines. With this edition, a critical care nursing-centric section has been added. This reflects the reality that intensive care medicine has inevitably become more interdisciplinary and collaborative.

The seventh edition is approximately the same length as the previous edition. To make this happen, we challenged every section editor and author to carefully balance edited materials emphasizing new evidence-based as well as state-of-the-art information by discarding outdated information. All of our section editors and chapter authors have done a superb job meeting this challenge. All chapters in every section have been updated with recent references and other materials that reflect current information, techniques, and principles. New chapters have been added to reflect emerging areas of interest. As stated earlier, an entirely new section has been added on "Nursing Issues in the ICU" that was ably coedited by Dorrie Fontaine and Shawn Cody. This section was meant to focus on issues related to collaboration, healthy work environments, and the expanding roles of nurses not the specifics of nursing care that have been brilliantly covered in textbooks of ICU nursing; and Dorrie and Shawn have admirably succeeded in this regard. Another new section on "Critical Care Consequences of Weapons (or Agents) of Mass Destruction" reflects the changing realities of our world and has been ably edited by Larry Mohr.

Evidenced-based medicine continues to play an ever more prominent role in all branches of medicine including critical care. With this in mind, we have asked every chapter author to make recommendations that specifically reflect recent trials with a particular emphasis on randomized prospective controlled trials. Authors have summarized such evidence, when the data have allowed, with helpful tables.

In medical intensive care, important changes and advances have occurred since the publication of the sixth edition. These include managing our ICUs according to the following guiding principles: (i) making our ICUs safer for our patients; (ii) decreasing variability by following clinical practice guidelines based upon the best available evidence to ensure better outcomes for our patients; and (iii) doing more with less to decrease the cost of caring for our patients. While these principles have always been espoused, it has become clear that we must more consistently follow them. With respect to specific issues, the day-to-day use of ultrasonography by critical care specialists is a very recent change and this is reflected in the liberal use of ultrasonographic images throughout the book and a new chapter entitled Interventional Ultrasound; these are prominently featured in the procedure and monitoring chapters. Moreover, there is an imperative to increasingly utilize information technology in the everyday practice of intensive care medicine. This not only includes using electronic medical records, computer physician order entry, and clinical decision support tools but also tele-ICU. All of these issues are covered in the section entitled "Contemporary Challenges in the Intensive Care Unit" edited by Craig Lilly.

In coronary care, rapid advances in techniques and interventions continue to occur. These changes are reflected in the "Cardiovascular Problems and Coronary Care" section of the seventh edition. It is interesting to see how cardiovascular intensive care has dramatically changed since the publication of our first few editions, as the advances in cardiology and cardiac surgery became known from the large, multicenter, randomized controlled clinical trials. We welcome Akshay Desai who has joined Patrick O'Gara as co-section editor for this section.

Equally important advances have occurred in surgical critical care, including new therapies and techniques in a variety of conditions treated in this environment. Our "Surgical Problems in the Intensive Care Unit" section remains a great strength of this book. Fred Luchette did his usual magnificent job on this edition. We recognize Arthur Trask and Stephen Barnes who have done an admirable job of updating the "Shock and Trauma" section of the textbook as well.

While our textbook has been updated and broadened to include new understandings, information and techniques, our goal has been to maintain the practical, clinically oriented approach that readers have come to expect from previous editions. Our editorial focus remains on clinically relevant studies and information that readers have found so useful in the previous six editions.

As in the past, our textbook opens with a detailed section on commonly performed "Procedures and Techniques in the Intensive Care Unit." This section, along with the "Minimally Invasive Monitoring" section, has also been simultaneously published as a smaller book entitled "Procedures, Techniques, and Minimally Invasive Monitoring in Intensive Care Medicine. All chapters in these sections have been updated with new figures and descriptions of techniques which have been added to reflect changes since the sixth edition of the textbook. We are indebted that section editors Stephen Heard and Alan Lisbon who have done a superb job on these sections.

The "Pharmacology, Overdoses, and Poisoning" section, consisting of 29 chapters, remains a great strength of this book and essentially represents a textbook on these topics embedded into our larger book. In this edition, we welcome new section editors Luke Yip and Kennon Heard who have joined Steven Bird as section editors for this outstanding and comprehensive section.

Because intensive care cannot be divorced from public policy, we continue to emphasize this with a major section of our textbook entitled "Contemporary Challenges in the Intensive Care Unit." This section includes not only more ethical and legal issues but also issues related to ICU organization and management, economics, safety, and information technology. With this edition, we welcome Craig Lilly, who has done an outstanding job on this section.

Our team of section editors continue to do a wonderful job coordinating large bodies of information that comprise the core of modern intensive care. Many of our section editors have been with us for one or more editions. Richard Ellison III (Infectious Disease), Neil Aronin (Endocrinology), Stephanie Levine (Transplantation), Dominic Nompleggi (Metabolism/Nutrition), Mark Madison (Pulmonary), John Querques (Psychiatry), and Joseph Frassica (Appendix, Calculations Commonly used in Critical Care) all fall into this category and have done their usual, excellent job. A new table on Antidotes has been added to the Appendix based on the efforts of Luke Yip, Jeremy Helphenstine, Jerry Thomas, and Ian Ball.

Some new section editors have joined us for the seventh edition and done great work. In addition to the individuals that we have already mentioned, we would like to specifically acknowledge the excellent efforts by the following new section editors or co-section editors: Pang-Yen Fan (Renal), Dominic Nompleggi (Gastrointestinal Problems), Patrick Fogarty (Hematologic Problems), David Paydarfar (Neurologic Problems), David Harlan (Endocrine Problems), and Nancy Liu (Rheumatologic, Immunologic and Dermatologic Problems).

As with previous editions, our emphasis remains on clinical management. Discussions of basic pathophysiology are also included and guided and supplemented by extensive references to help clinicians and researchers who wish to pursue more in-depth knowledge of these important areas. When therapies reflect institutional or individual bias or are considered controversial, we have attempted to indicate this.

We hope and believe that the outstanding efforts of many people over the past 4 years have continued to result in an evidence-based and state-of-the-art and comprehensive textbook that will elucidate the important principles in intensive care and will continue to guide and support the best efforts of practitioners in this challenging environment in their ongoing efforts to diagnosis and treat complicated diseases and relieve human suffering.

Richard S. Irwin, MD, Master FCCP
James M. Rippe, MD

ACKNOWLEDGMENTS

Numerous outstanding individuals have made significant contributions to all phases of writing and production of this textbook and deserve special recognition and thanks. First and foremost is our managing editor, Elizabeth Grady. Beth literally lives and breathes this textbook as it works its way through the production cycle every 4 years. She is the guiding and organizing force behind this textbook. It would simply not be possible without Beth's incredible organizational skills, good humor, and enormous energy. She has guided this book through six editions—this book is as much hers as it is ours.

Our administrative assistants, office assistant, and clinical coordinators, Carol Moreau, Debra Adamonis, Karen Barrell, Mary Garabedian, and Cynthia French have helped us continue to coordinate and manage our complex professional and personal lives and create room for the substantial amount of time required to write and edit. Our section editors have devoted enormous skill, time, and resources to every edition of this textbook. We have very much appreciated their deep commitment to this book and to advancing the field of intensive care medicine.

Our editors at Lippincott Williams & Wilkins including Brian Brown, executive editor, have been a source of great help and encouragement. As with the last edition, Nicole Dernoski continues to be extremely helpful and accommodating in supervising and coordinating all phases of production in an outstanding way.

Lastly, we are grateful to Indu Jawwad and her staff for the outstanding job they have done copyediting the manuscript for this edition.

Our families support our efforts with unfailing encouragement and love. To them, and the many others who have helped in ways too numerous to count, we are deeply grateful.

Richard S. Irwin, MD, Master FCCP
James M. Rippe, MD

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SECTION XVII ■ PSYCHIATRIC ISSUES IN INTENSIVE CARE

SECTION XVIII ■ NURSING

PATRICK F. FOGARTY

CHAPTER 108 ■ DISORDERS OF HEMOSTASIS IN CRITICALLY ILL PATIENTS

JEREMIAH BOLES AND ALICE D. MA

Disorders of hemostasis are common in critically ill patients. This chapter will review hemostasis, pathophysiology of commonly encountered congenital and acquired bleeding disorders along with their associated symptoms, laboratory findings, and management.

REVIEW OF NORMAL HEMOSTASIS

Hemostasis can be broken into a series of steps occurring in overlapping sequence. Primary hemostasis refers to the interactions between the platelet and the injured vessel wall, culminating in the formation of a platelet plug. The humoral phase of clotting, or secondary hemostasis, encompasses a series of enzymatic reactions, resulting in a hemostatic fibrin plug. Finally, fibrinolysis and wound repair occur. Each of these steps is carefully regulated, and perturbations can predispose to either hemorrhage or thrombosis. Depending on the nature of the defect, the hemorrhagic or thrombotic tendency can be either profound or subtle.

Primary hemostasis begins at the site of vascular injury, with platelets adhering to the subendothelium, utilizing interactions between molecules such as collagen and von Willebrand factor (vWF) in the vessel wall with glycoprotein (GP) receptors on the platelet surface. Upon exposure to agonists present at a wounded vessel, signal transduction leads to platelet activation. Via a process known as inside-out signaling, the platelet membrane integrin $\alpha_{2b}\beta_3$ (also known as GP IIbIIIa) undergoes a conformational change to be able to bind fibrinogen, which cross-links adjacent platelets, leading to platelet aggregation. Secretion of granular contents is also triggered by outside signals, potentiating further platelet activation (Fig. 108.1). Lastly, the surface of the platelet changes to serve as an adequate scaffold for the series of biochemical reactions resulting in thrombin generation.

Following platelet activation, a series of enzymatic reactions take place on phospholipid surfaces, culminating in the formation of a stable fibrin clot. Several models have attempted to make sense of these reactions. The cascade model was developed by two groups nearly simultaneously [1,2] and explained the extrinsic, intrinsic, and common pathways leading to fibrin formation (Fig. 108.2). While the cascade model accounts for the physiologic reactions underlying the prothrombin time (PT) and the activated partial thromboplastin time (aPTT), it fails to explain completely the bleeding diathesis seen in individuals deficient in factors XI, IX, and VIII, as well as the lack of bleeding in those deficient only in contact factors. A cell-based model of hemostasis has been developed to address these deficiencies. In this model, upon vascular injury, the membrane of a tissue factor (TF)-bearing cell such as an activated monocyte or fibroblast serves as a platform for generation of a small amount of thrombin and FIXa, which then serves to activate platelets and cleave FVIII from vWF. Newly formed FVIIIa participates in the tenase complex on the surface of activated platelets to form FXa that interacts with the FVa generated on the platelet surface to form the prothrombinase complex. This complex generates a large burst of thrombin which is sufficient to cleave fibrinogen, activate FXIII, and activate the thrombin activatable fibrinolysis inhibitor (TAFI), thus allowing for formation of a stable fibrin clot (Fig. 108.2).

Fibrinolysis leads to clot dissolution once wound healing has occurred, in order to restore normal blood flow. Plasminogen is activated to plasmin by the action of either tissue plasminogen activator (t-PA) or urokinase plasminogen activator (u-PA). Plasmin degrades fibrin and fibrinogen and can thus dissolve both formed clot as well as its soluble precursor. Plasmin is inhibited by a number of inhibitors, of which α_2-plasmin inhibitor is the most significant. Plasminogen activation is also inhibited by a number of molecules; chief among them is plasminogen activator inhibitor-1 (PAI-1). Lastly, cellular receptors act to localize and potentiate or clear plasmin and plasminogen activators (see Chapter 111 for further discussion).

APPROACH TO THE BLEEDING PATIENT

Physicians in the intensive care unit (ICU) often encounter bleeding patients and it can be difficult to identify which of these patients require further evaluation. Patients who experience bleeding that is excessive, spontaneous, or delayed following surgery or tissue injury require further investigation, which must begin with a thorough clinical history. A bleeding history should assess a patient's exposure and response to all hemostatic challenges in the past such as trauma, surgery, and childbirth. Characterization of menses in females also may be revealing. Several bleeding assessment tools have been developed and are useful in the evaluation for an underlying coagulopathy, particularly von Willebrand disease (vWD) [3]. This history should also identify coexisting medical conditions such as liver, kidney, or thyroid disorders. A careful medication history is also important, including use of all over-the-counter medications which may contain aspirin, as well as any herbal preparations. Also of cardinal importance is an evaluation for a family history of abnormal bleeding. An inherited or congenital bleeding disorder is suggested by abnormal bleeding with onset shortly after birth and persistence throughout life. It is further supported by a family history with a consistent genetic pattern. However, it is important to note that a negative family history does not exclude a congenital bleeding disorder. For instance, approximately one third of all cases of hemophilia A arise from spontaneous mutations. Many of the rare coagulation disorders, including deficiency of factors II, V, VII, X,

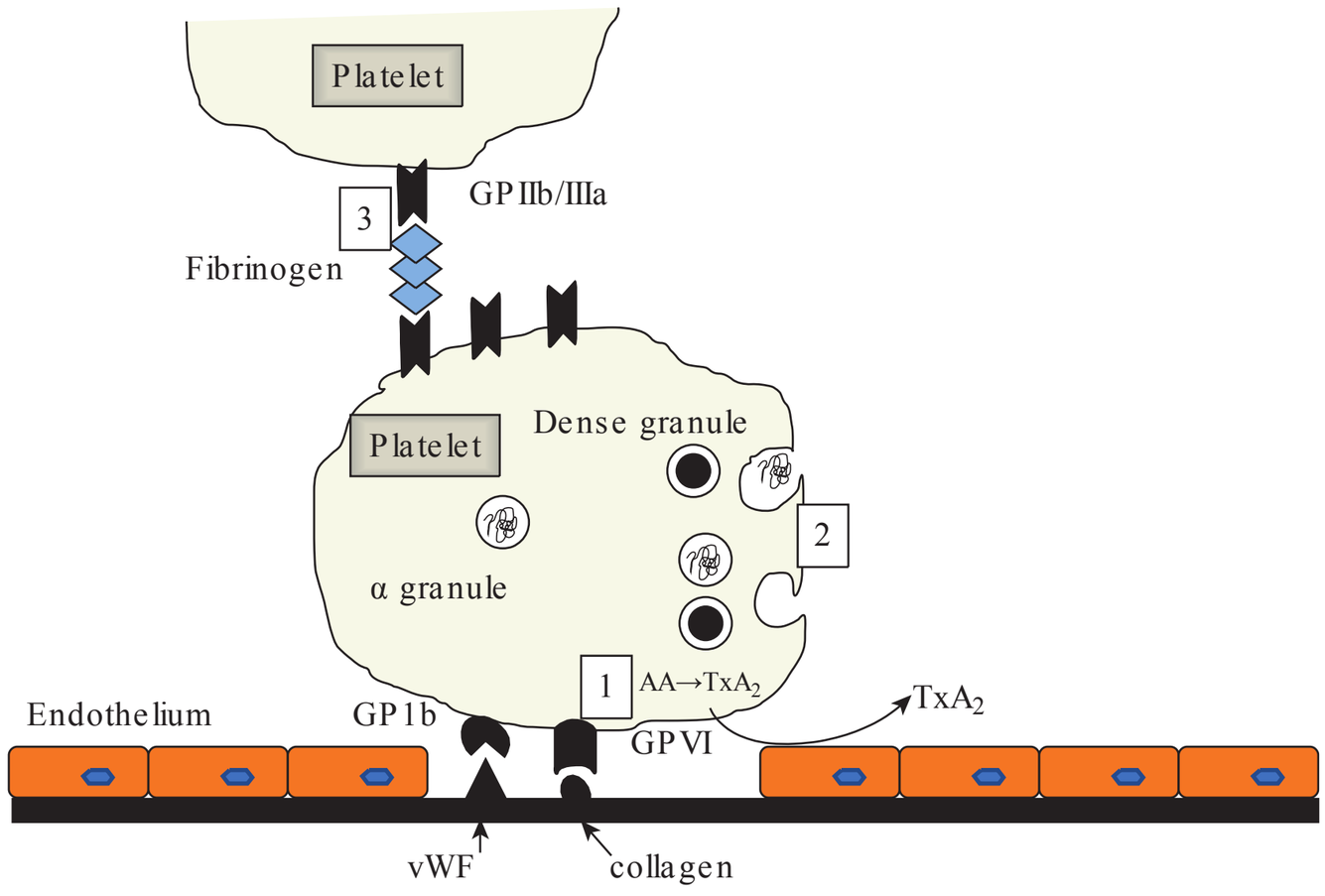


FIGURE 108.1. Primary hemostasis. (1) Exposure of subendothelium at sites of vascular disruption results in platelet adhesion via GPIb and GP VI with exposed von Willebrand factor (vWF) and collagen, respectively. Following platelet adhesion TxA_2 is produced and released which promotes vasoconstriction and platelet aggregation. (2) Platelet adhesion also results in fusion of cytoplasmic granules to the plasma membrane. Release of alpha and dense granules activates nearby platelets. (3) Platelet activation results in exposure of GPIIb/IIIa on the platelet surface allowing fibrinogen to cross bridge platelets resulting in a platelet plug.

as well as vWD type 2 N, among others, are inherited in an autosomal recessive fashion, and the parents of the patient may be entirely asymptomatic.

A bleeding history should also ascertain past sites/mechanisms of bleeding. Surgical bleeding in patients with an underlying hemorrhagic condition is typically described as "diffuse oozing," without the readily identifiable bleeding source seen with a surgical mishap such as a severed vessel. Patients with platelet disorders typically manifest mucocutaneous bleeding such as gingival bleeding and epistaxis as well as menorrhagia, petechiae, and ecchymoses. Platelet defects impact primary hemostasis and therefore the bleeding in these disorders is often immediate following surgery or trauma, whereas delayed bleeding is more classically associated with coagulation disorders. Patients with coagulation defects typically present with hemorrhages into soft tissues such as muscles and joints.

A physical examination should pay particular attention to the skin, joints, mucosal surfaces, and liver and spleen size.

LABORATORY ASSAYS OF PRIMARY AND SECONDARY HEMOSTASIS

While the history and physical examination can increase suspicion for the presence of a bleeding disorder, laboratory confirmation is required for precise diagnosis and treatment.

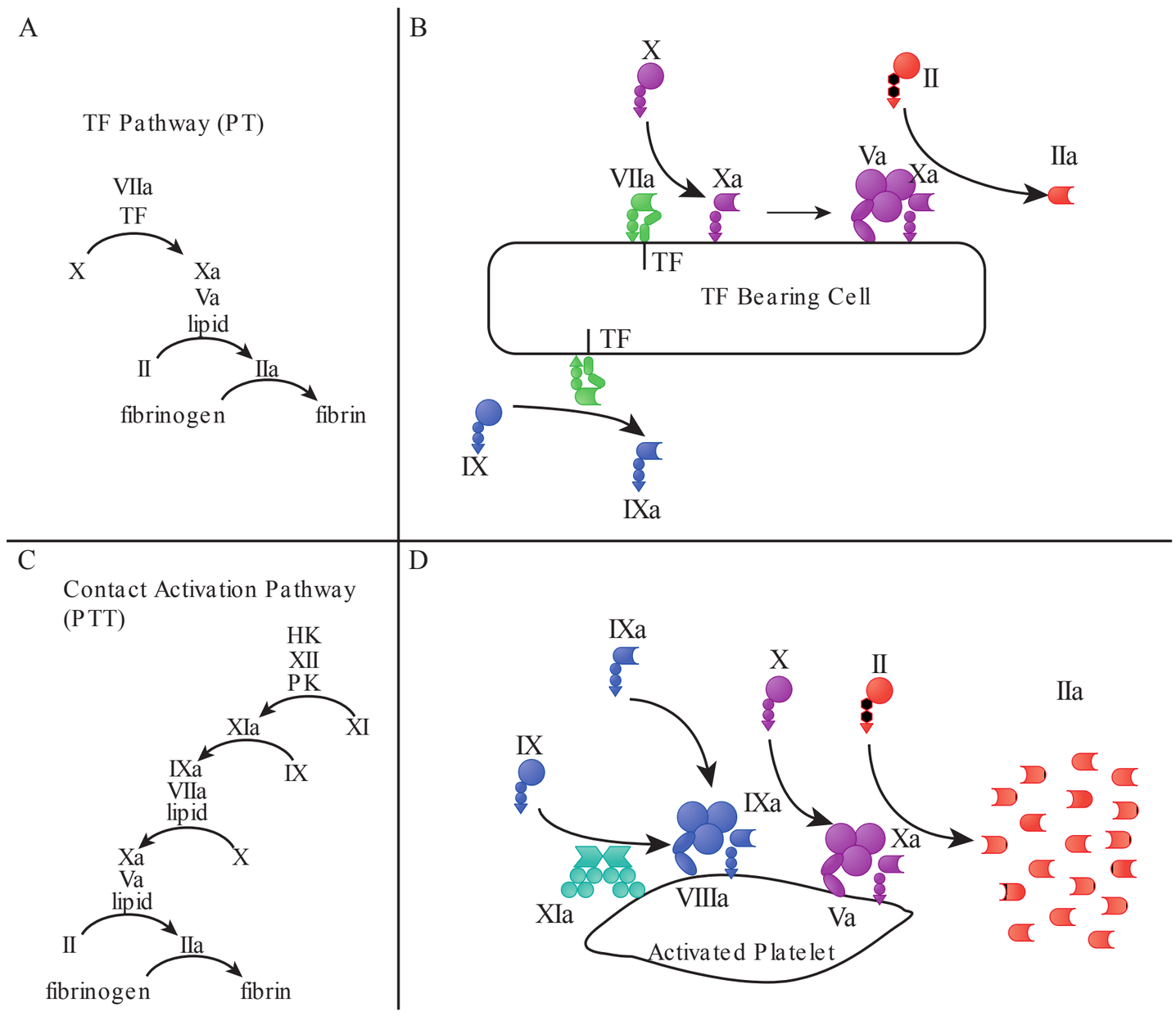


FIGURE 108.2. Secondary hemostasis. **A:** Tissue factor (TF) pathway cascade model of coagulation—basis for prothrombin time (PT) laboratory assay. **B:** Circulating FVIIa binds TF on a TF-bearing cell. TF/FVIIa along with calcium (Ca) and phospholipid (lipid) form the "extrinsic tenase" complex and converts FX to FXa. FXa combines with FVa, calcium, and phospholipid, "prothrombinase" complex, to activate FII to FIIa which in turn converts fibrinogen into fibrin. **C:** Contact activation pathway model of coagulation—basis for partial thromboplastin time (PTT) laboratory assay. **D:** On an activated platelet surface, FXIa activates FIXa. FIXa is also formed on the surface of a TF-bearing cell (B). FIXa, along with FVIIIa, Ca, and lipid, constitute the "intrinsic tenase" complex. This complex converts FX to FXa with subsequent FIIIa generation through the prothrombinase complex. (Courtesy of Dougald Monroe.)

Laboratory evaluation is particularly crucial in individuals who are suspected of having a bleeding disorder but in whom prior bleeding is absent, such as those with mild congenital bleeding disorders who never previously underwent a sufficient hemostatic challenge, or those with acquired hemorrhagic disorders.

Initial Evaluation of Primary Hemostasis—Platelet Function

An assessment of a patient's platelet count is fundamental in evaluating primary hemostasis. This is typically part of a complete blood count (CBC). Reduced platelet counts, or thrombocytopenia, may be seen in a large number of acquired and congenital conditions. Evaluation and management of thrombocytopenia is further discussed in Chapter 109.

An evaluation of the peripheral smear is also cardinal in any evaluation of a bleeding patient. It allows one to assess platelet size and morphology, presence of platelet clumping (pseudothrombocytopenia), leukocyte inclusions, and red cell fragments, among other aberrancies, which may further direct workup and treatment.

Traditionally, platelet function was evaluated by bleeding time (BT). However, many institutions have discontinued using this test given the difficulty in standardization. Furthermore, the BT has been shown to be an inadequate predictor of bleeding, particularly in preoperative risk assessment [4]. More recently, automated tests have been developed to assess platelet function. The most widely used is the platelet function analyzer (PFA-100®). This assay measures the time required (closure time) for flowing whole, citrated blood to occlude an aperture in a membrane impregnated with a combination of either collagen and epinephrine or collagen and adenosine diphosphate (ADP). Closure time is affected by platelet count, hematocrit, platelet function, and vWF [5]. The PFA-100® appears to assess platelet function with greater sensitivity and reproducibility than the BT; however, a recent position statement from the Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis noted that although the PFA-100® is abnormal in some platelet disorders, it was not felt to have sufficient sensitivity or specificity to be used as a screening tool for platelet disorders [6].

Evaluation of Secondary Hemostasis—Coagulation

The PT and the aPTT are assays performed on citrated plasma, which require enzymatic generation of thrombin on a phospholipid surface. Prolongation of the PT and the aPTT can be seen in individuals with either deficiencies of, or inhibitors to, humoral clotting factors, though not all patients with prolongations of these assays will have bleeding diatheses (Table 108.1).

The PT measures the time needed for formation of an insoluble fibrin clot once citrated plasma has been recalcified and thromboplastin has been added, indicating activity of factors VII, V, X, and II and fibrinogen. It commonly is used to monitor anticoagulation with vitamin K antagonists such as warfarin. Since thromboplastin from various sources and different lots can affect the rates of clotting reactions, the International Normalized Ratio (INR) measurement was developed

TABLE 108.1

LABORATORY TEST ABNORMALITIES IN COMMON ACQUIRED AND CONGENITAL BLEEDING DISORDERS

	Acquired bleeding disorders	Congenital bleeding disorders
PT elevated, aPTT wnl	Liver disease DIC Vitamin K deficiency Vitamin K antagonists (e.g., warfarin)	FVII deficiency
PT wnl, aPTT elevated	Heparin Lupus inhibitor Acquired FVIII inhibitor	Hemophilia A and B FXI deficiency Severe vWD
Both PT and aPTT elevated	Heparin overdose Warfarin overdose FVI inhibitors FX inhibitors Severe DIC Severe vitamin K deficiency Severe liver disease Direct thrombin inhibitors	Afibrinogenemia Hypo- or dysfibrino-genemia Prothrombin deficiency FV deficiency Combined deficiency of FV and FVIII
Both PT and aPTT wnl	LMWH therapy Fondaparinux therapy Antiplatelet agents Acquired vWD Scurvy Acquired thrombocytopenia	vWD FXIII deficiency Congenital platelet dysfunction Congenital thrombocytopenia Collagen disorders (e.g., Ehlers–Danlos syndrome)

wnl, within normal limits; DIC, disseminated intravascular coagulation; LMWH, low-molecular-weight heparin; PT, prothrombin time; PTT; partial thromboplastin time; vWD, von Willebrand disease.

to avoid some of this variability in PT measurement. Each batch of thromboplastin reagent has assigned to it a numerical International Sensitivity Index (ISI) value, which is used in the formula:

$$INR = (PT_{patient} / PT_{normal\ mean})^{ISI}$$

The INR is less predictive of bleeding in patients with liver disease, and can be inaccurate in patients with lupus anticoagulants that are strong enough to affect the PT.

The aPTT tests the activity of factors XII, XI, IX, VIII, X, V, and II, and fibrinogen, high-molecular-weight kininogen (HMWK), and plasma prekallikrein (PK) [7]. Citrated plasma is recalcified, and phospholipids (to provide a scaffold for the clotting reactions) and an activator of the intrinsic system such as kaolin, celite, or silica are added. The reagents used show variable sensitivities to inhibitors such as lupus anticoagulants and heparin, and to deficiencies (if any) in involved clotting factors, and normal ranges will vary from laboratory to laboratory. aPTT values that are vastly different from one laboratory to another should prompt suspicion of a lupus anticoagulant.

The Thrombin Clotting Time and Reptilase Time

The thrombin clotting time (TCT) or thrombin time (TT) measures the time needed for clot formation once thrombin is added to citrated plasma. Thrombin enzymatically cleaves fibrinopeptides A and B from the α- and β-chains of fibrinogen, allowing for polymerization into fibrin. The TT is prolonged in the presence of any thrombin inhibitor such as heparin, lepirudin, or argatroban; by low levels of fibrinogen or structurally abnormal fibrinogen (dysfibrinogens); and by elevated levels of fibrinogen or fibrin degradation products, which can serve as nonspecific inhibitors of the reaction. Patients with paraproteins can have a prolonged TT because of the inhibitory effect of the paraprotein on fibrin polymerization.

Reptilase is snake venom from *Bothrops atrox* which also enzymatically cleaves fibrinogen. Reptilase cleaves only fibrinopeptide A from the α-chain of fibrinogen, but fibrin polymerization still occurs. Reptilase time (RT) is not affected by heparin but may be more sensitive than the TT to the presence of a dysfibrinogenemia.

Mixing Studies

Mixing studies are used to evaluate prolongations of the aPTT (less commonly the PT or the TT) and are useful in making the distinction between an inhibitor and a clotting factor deficiency. The patient's plasma is mixed 1:1 with normal control plasma, and the assay is repeated (with or without prolonged incubation at 37°C). Correction of the clotting test signifies factor deficiency, since the normal plasma will supply the deficient factor. Incomplete correction of the clotting test after mixing suggests the presence of an inhibitor, since an inhibitor will prolong clotting in normal plasma. Incomplete correction can sometimes be seen with nonspecific inhibitors such as lupus anticoagulants, elevated fibrin split products, or a paraprotein. Less commonly, deficiencies of multiple clotting factors can lead to incomplete correction of the mixing study, since the mixing study was designed to correct deficiency of a single factor.

Tests of specific factor activity levels as well as evaluation for vWD will be discussed in the following sections.

CONGENITAL DISORDERS OF HEMOSTASIS

Due to a requirement for specialized management, all cases of suspected or proven congenital hemostatic defects require consultation with a hematologist upon admission to the critical care setting.

Von Willebrand Disease

It has been estimated that lower-than-reference levels of vWF occur in 1% of the population worldwide and therefore vWD is the most common congenital bleeding disorder [8]. However, only a fraction of the aforementioned individuals are symptomatic (approximately 5% of those with low levels) [9]. vWD is inherited in an autosomal manner with the more common type I disease being autosomal dominant.

vWD constitutes a quantitative or qualitative deficiency in vWF, and is divided into three subtypes according to the pathophysiology. Types 1 and 3 are the result of a partial (type 1) or virtually a complete (type 3) quantitative deficiency of vWF, while type 2 is a qualitative defect in vWF. Type 1 vWD represents the most common subtype accounting for approximately 70% of patients, while type 2 accounts for 15% to 20% and type 3 for only 2% to 5% of vWD patients [10].

Because bleeding symptoms in persons with vWD may be absent or overlooked until a major hemorrhage due to surgery or trauma has occurred, the diagnosis should be considered in an ICU patient with otherwise unexplained excessive bleeding, particularly if there is a significant family history including an autosomal pattern of inheritance. The most common historical bleeding symptoms include epistaxis, increased bleeding after dental extractions, and menorrhagia. A validated bleeding assessment tool has been developed to screen outpatients who may benefit from formal vWD laboratory testing [3], but its usefulness in the critical care setting has not been established.

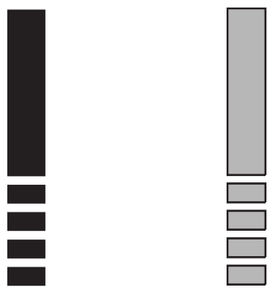
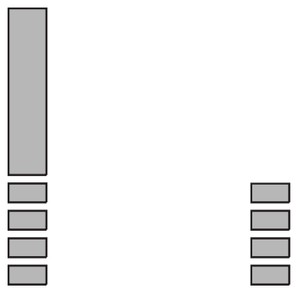
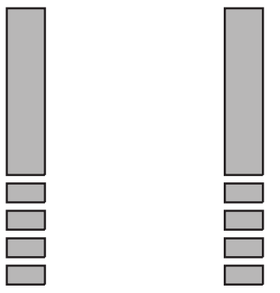
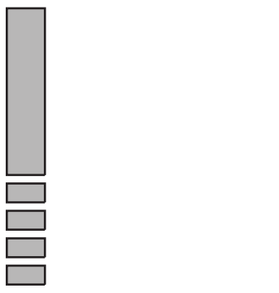
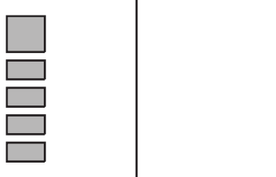
A formal diagnosis of vWD should be based on three components: (a) a history of excessive bleeding, either spontaneous mucocutaneous and/or postsurgical, (b) a positive family history for excessive bleeding, and (c) confirmatory laboratory testing. Diagnostic tests for vWD, reviewed elsewhere [11], should be performed in a specialized laboratory and are summarized in Table 108.2.

The goals of treatment in vWD are to correct the quantitative or qualitative deficiencies in vWF, platelets, and FVIII. Treatment options include desmopressin (DDAVP), vWF-containing concentrates, and/or antifibrinolytics. See Tables 108.3 and 108.4 for general treatment guidelines.

In normal volunteers, DDAVP increases plasma levels of FVIII, vWF, and tissue plasminogen activator [12]. It may be given IV or SQ [13]. When given intravenously, the FVIII and vWF levels are usually increased three- to fivefold above basal levels within 30 minutes. vWD patients should undergo a DDAVP trial to gauge their individual response since there is considerable interindividual variability. Dosing of DDAVP for vWD is generally recommended at 0.3 μg per kg (IV or SQ), or 300 μg intranasally, which can be repeated at intervals of 12 to 24 hours. Tachyphylaxis (due to depletion of FVIII/vWF from repeated endothelial exocytosis into plasma) following repeated dosing is expected; DDAVP given as a second dose is 30% less effective than the first dose [14]. For this reason, and due to the risk of hyponatremia (which can lead to seizures), serial dosing should be limited to two to three doses in a 72-hour period with concurrent free water restriction and monitoring of serum sodium levels. DDAVP is most effective in type 1 vWD. It is relatively contraindicated in type 2B vWD because of the transient induction of thrombocytopenia [15]. Patients

TABLE 108.2

EXPECTED LABORATORY VALUES IN vWD FROM THE NHLBI

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	PLT-vWD[a]
vWF:Ag	N	L, ↓ or ↓↓	↓ or L	↓ or L	↓ or L	N or L	Absent	↓ or L
vWF:RCo	N	L, ↓ or ↓↓	↓↓ or ↓↓↓	↓↓	↓↓	N or L	Absent	↓↓
FVIII	N	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	1-9 IU/dL	N or L
RIPA	N	Often N	↓	Often N	↓	N	Absent	Often N
LD-RIPA	Absent	Absent	Absent	↑↑↑	Absent	Absent	Absent	↑↑↑
PFA-100® CT	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
BT	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
Platelet count	N	N	N	↓ or N	N	N	N	↓
vWF multimer pattern	N	N	Abnormal	Abnormal	N	N	Absent	Abnormal
								

[a]The symbols and values represent prototypical cases. In practice, laboratory studies in certain patients may deviate slightly from these expectations. L, 30–50 IU/dL; ↓, ↓↓, ↓↓↓, relative decrease; ↑, ↑↑, ↑↑↑, relative increase; BT, bleeding time; FVIII, factor VIII activity; LD RIPA, low-dose ristocetin-induced platelet aggregation (concentration of ristocetin ≤ 0.6 mg/mL); N, normal; PFA-100® CT, platelet function analyzer closure time; RIPA, ristocetin-induced platelet aggregation; vWF, von Willebrand factor; vWF:Ag, vWF antigen; vWF:RCo, vWF ristocetin cofactor activity.
Reprinted from The National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation, and Management of von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5832, 2008.

with type 3 vWD are usually unresponsive to DDAVP. Certain hemophilia treatment centers caution against use of DDAVP in patients with coronary artery disease, since this agent may also activate platelets.

Antifibrinolytic agents (epsilon aminocaproic acid and tranexamic acid) can be used alone or as adjunctive treatment in vWD patients with mucosal bleeding. These drugs inhibit fibrinolysis by inhibiting plasminogen activation, thereby promoting clot stability. They are contraindicated in the setting of gross hematuria as resultant ureteral obstruction by insoluble clot has been described. Given a concern for thrombosis, antifibrinolytics should be avoided in patients with

TABLE 108.3

DOSING GUIDELINES FOR VON WILLEBRAND DISEASE (vWD) TREATMENT

Medication	Dose	Comments
DDAVP	Nasal spray: 300 µg (1 spray in each nostril) If weight < 50 kg 150 µg (1 spray in 1 nostril) IV: 0.3 µg/kg (not to exceed 20–25 µg)	Most useful in type 1 vWD, ineffective in type 3. Requires challenge to document efficacy. Relatively contraindicated in type 2B as may exacerbate thrombocytopenia May repeat dose in 12 h and/or 24 h. Tachyphylaxis occurs with repeat dosing. Due to risk of hyponatremia, if dosing serially, limit doses to no more than 2–3 in a 72-h period, fluid restrict, and follow serum sodium levels. Avoid in patients with coronary disease.
Antifibrinolytic agents: epsilon-aminocaproic acid (EACA)	50 mg/kg PO up to q 6h (lower doses may be effective) or 1 g/h IV continuous infusion Do not exceed 24 g/24 h	Especially useful for mucocutaneous bleeding, especially for dental procedures May be used as adjunctive treatment (DDAVP, factor concentrates)
Tranexamic acid	25 mg/kg q 8 h (not yet available in the United States)	Avoid in upper urinary tract bleeding
vWF-containing FVIII concentrates (e.g., Humate-P, Alphanate)	60–80 RCoF U/kg as an initial dose, then 40–60 u/kg IV every 12 h (see Table 108.4)	FVIII activity levels are often used in the monitoring of response to vWF-containing products as real-time vWF activity measures are not always available Dosed in RCoF units. Individual product is labeled with ratio of RCoF units:FVIII

DDAVP, desmopressin; vWD, von Willebrand disease; vWF, von Willebrand factor; RCoF, ristocetin cofactor.

TABLE 108.4

SUGGESTED INITIAL DOSING OF vWF CONCENTRATES FOR PREVENTION OR MANAGEMENT OF BLEEDING

	Major surgery/bleeding
Loading dose[a]	60–80 RCoF U/kg
Maintenance dose	40–60 RCoF U/kg, typically every 12 h initially
Monitoring	vWF:RCo and FVIII trough and peak, at least daily
Therapeutic goal	Trough vWF:RCo and FVIII > 50 IU/dL for 7–14 d
Safety parameter	Do not exceed vWF:RCo 200 IU/dL or FVIII 250–300 IU/dL
May alternate with DDAVP for latter part of treatment	
	Minor surgery/bleeding
Loading dose[a]	30–60 U/kg
Maintenance dose	20–40 U/kg every 12–48 h
Monitoring	vWF:RCo and FVIII trough and peak, at least once
Therapeutic goal	Trough vWF:RCo and FVIII > 50 IU/dL for 3–5 d
Safety parameter	Do not exceed vWF:RCo 200 IU/dL or FVIII 250–300 IU/dL
May alternate with DDAVP for latter part of treatment	

[a]Loading dose is in vWF:RCo IU/dL.
Adapted from The National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation, and Management of von Willebrand Disease. Bethesda, MD: National Institutes of Health Publication 08-5832, 2008.

prothrombotic conditions, disseminated intravascular coagulation (DIC), or when receiving prothrombin complex concentrates (PCCs).

vWF factor-containing FVIII concentrates are appropriate for patients with severe vWD or in situations when other therapies (including DDAVP) are ineffective and are preferred to cryoprecipitate, which contains vWF, but has not undergone viral inactivation. When used in the treatment of vWD, they are dosed in ristocetin cofactor (RCoF) units, as opposed to FVIII units (Table 108.4). Limited data suggest a role for rFVIIa in patients with type 3 vWD who have developed alloantibodies to vWF [16].

The National Heart Lung and Blood Institute has recently published guidelines for the diagnosis, evaluation, and management of vWD [17].

Hemophilia

The hemophilias are congenital bleeding disorders characterized by X-linked inheritance and result in a deficiency of FVIII (hemophilia A) or FIX (hemophilia B). In the United States, they have a combined incidence of 1 in 5,000 male births. Hemophilia A is more common than hemophilia B and accounts for approximately 80% of cases. Since hemophilia is an X-linked disorder, all daughters of affected males are obligate carriers and all sons are healthy. Females may rarely manifest bleeding symptoms if they (a) are the homozygous offspring from a carrier mother and affected father, (b) have a high degree of lyonization, or (c) are a carrier with concomitant Turner's syndrome (XO).

The clinical phenotype of hemophilia patients depends on the residual level of circulating procoagulant protein (FVIII or FIX). It is possible to differentiate three degrees of clinical severity: (a) mild hemophilia (5% to 50% factor activity) in which bleeding is prolonged but typically only occurs following trauma or surgery, (b) moderate hemophilia (1% to 5% factor activity) in which prolonged bleeding follows minor trauma, and (c) severe hemophilia (< 1% factor activity) where patients experience spontaneous hemorrhage into joints (hemarthrosis) and muscles.

In severe and moderate hemophilia, the PT is normal and the aPTT is prolonged. However, the PTT may be normal in patients with mild hemophilia whose residual factor activity is > 20%. If the aPTT is prolonged, it should correct with a mixing study, since hemophilia is a factor deficiency syndrome. Specific factor assays should be performed to confirm a diagnosis of hemophilia A or B.

The management of most cases of hemophilia, thanks to the availability of replacement clotting factor concentrates, occurs in the outpatient setting, but individuals who previously have escaped diagnosis (mild or moderate hemophilia) or who have sustained major trauma or complications from a bleeding episode (compartment syndrome) may present to critical care. If not previously diagnosed, hemophilia should be suspected in male patients who have a personal history of bleeding into joints or muscles, a history of excessive bleeding upon surgical challenge, and/or a positive sex-linked family history of bleeding.

Hemarthrosis, a hallmark of hemophilia, accounts for approximately 85% of all bleeding events in severe hemophilia and most commonly involves the ankles, knees, and elbows [18]. Intramuscular hematomas in persons with hemophilia may expand to the point where blood flow is compromised to surrounding neurovascular structures resulting in tissue gangrene and compartment syndrome; the condition requires surgery and aggressive clotting factor replacement therapy [19] (Table 108.5). Gastrointestinal bleeding is uncommon in hemophilia. However, patients with an underlying structural lesion may present with hematemesis, hematochezia, or melena. Hemophilia patients who present with evidence for gastrointestinal bleeding should have a complete endoscopic evaluation to assess for and treat any underlying lesion. Approximately 90% of persons with severe hemophilia will develop hematuria during their life, although the condition is typically painless, benign, and unassociated with a structural lesion. As discussed earlier, antifibrinolytic agents are contraindicated in patients with genitourinary bleeding.

TABLE 108.5

RECOMMENDED HEMOSTATIC LEVELS IN HEMOPHILIA[a]

Clinical situation	Hemophilia target factor activity (%)[a]
Mild hemorrhage (joint, muscle)	30–40
Mucosal hemorrhage (oral, dental)	30–40 with EACA
Major hemorrhage	> 50
Life-threatening hemorrhage or perioperative management (major and orthopedic procedures)	100

[a]Minimum recommended goal factor activity levels.
EACA, epsilon-aminocaproic acid.

Hemorrhage into head and neck structures is a medical emergency in persons with hemophilia. Retropharyngeal hematoma, which may occur spontaneously or following dental or surgical procedures, may present with inability to control saliva, neck swelling, and pain. If untreated, it may result in airway compromise and in some cases may require tracheostomy. Hemorrhage into the central nervous system is a severe and potentially fatal (albeit rare) complication of hemophilia. Intracranial hemorrhage (ICH) may occur spontaneously in severe hemophilia or as the result of trauma. Prompt recognition of ICH is paramount and factor replacement therapy should be given immediately while the diagnostic workup is underway (Table 108.5).

The approach to treating major bleeding episodes in hemophilia A and B is similar. The clinical scenario dictates the target factor activity level (Table 108.5). For example, an ICH requires a target activity level of 100% initially, while levels of 30% to 40% may be sufficient for minor bleeds such as uncomplicated hemarthrosis. Prior to completion of the diagnostic (radiologic or otherwise) workup, clotting factor concentrate should be administered immediately to a person with hemophilia and a suspected life- or limb threatening bleed. Plasma-derived and recombinant factor concentrates [20] contain much higher concentrations of the desired factor compared to fresh frozen plasma (FFP) or cryoprecipitate. If possible, avoidance of FFP or cryoprecipitate is advised to avoid volume overload, transfusion-related lung injury (TRALI), and potential viral transmission (see Chapter 114).

DDAVP may be used instead of factor concentrate in selected patients with mild hemophilia A who have minor bleeding or a requirement for an enhanced FVIII activity level prior to a short-lived bleeding challenge. Any mild hemophilia A patient should undergo a DDAVP trial to gauge his or her individual response in lieu of assuming efficacy of the agent. FVIII levels in plasma increase two- to six-fold following administration. For mild hemophilia A, the recommended dose is 0.3 µg per kg (IV or SQ) or 300 µg intranasally; as previously discussed, tachyphylaxis and hyponatremia may develop after serial dosing.

Antifibrinolytic agents are a useful adjunctive treatment in hemophilia patients with mucosal bleeding. However, hemophilic patients with hematuria, DIC, receiving a PCC, or other prothrombotic conditions should not be treated with antifibrinolytics.

One of the most significant complications of hemophilia treatment is the development of an inhibitor. Inhibitors are alloantibodies against exogenously administered clotting factor that neutralize the factor. The development of a new inhibitor is more common in hemophilia A than in hemophilia B [21], in severe hemophilia, and among previously untreated patients (as opposed to adults who typically have been extensively exposed to clotting factor concentrate).

Inhibitors, if present at high titer, neutralize exogenous factor rendering factor concentrates ineffective. Therefore, an inhibitor should be suspected when administration of factor concentrate at a dose previously sufficient to achieve hemostasis, or improve bleeding, fails to do so. Once suspected, a Bethesda assay should be performed to document the titer of the inhibitor (reported in Bethesda units, BU). Of the two goals of treatment in patients with inhibitors, namely, to achieve adequate hemostasis and to eradicate the inhibitor, only the former is typically relevant to the critical care setting. Bleeding should be treated with bypassing agents, typically an activated prothrombin complex concentrate (aPCC) or rFVIIa [22]. If the titer is < 5 BU, high doses of FVIII or FIX may be given as initial treatment in cases of life- or limb-threatening bleeding episodes. In patients with a long-standing inhibitor, however, the anamnestic response negates factor activity after 5 to 7 days, at which point bypassing agents become necessary.

RARE CONGENITAL COAGULATION DISORDERS

Less Common Coagulation Factor Deficiencies

The hemophilias and vWD represent approximately 85% of congenital bleeding disorders. The remaining disorders will be briefly discussed next.

Disorders of Fibrinogen

Congenital fibrinogen disorders result from a quantitative (afibrinogenemia) or qualitative (dysfibrinogenemia) defect in fibrinogen synthesis. Congenital afibrinogenemia has a variable bleeding phenotype with the majority of patients experiencing moderate bleeding [23]. Afflicted individuals present typically in the neonatal period with umbilical stump bleeding or bleeding following circumcision [23]. Patients may also experience hemarthrosis, intramuscular hemorrhage, spontaneous abortion, mucosal surface bleeds, ICH, or spontaneous splenic rupture [24]. Heterozygotes are typically asymptomatic. The clinical phenotype in patients with congenital dysfibrinogenemia is variable and includes (a) asymptomatic (55%), (b) hemorrhagic (25%), (c) thrombotic (10% to 20%), or (d) a combination of both hemorrhagic and thrombotic complications (1% to 2%) [25]. Treatment of congenital fibrinogen disorders should be individualized given the clinical variability. In general, replacement therapy in the form of fibrinogen concentrates, cryoprecipitate, or (not recommended) FFP should be given to patients with a hemorrhagic presentation to achieve a goal fibrinogen level of 50 to 100 mg per dL [26].

Prothrombin (FII) Deficiency

Congenital prothrombin deficiency is characterized by a concordant decrease in prothrombin antigen and activity [27]. Aprothrombinemia has not been reported. Patients with hypoprothrombinemia present with severe hemorrhage including ICH, mucocutaneous bleeding, hemarthrosis, spontaneous abortions, and significant postoperative bleeding. Heterozygotes are usually asymptomatic; however, they may experience

increased postoperative bleeding [28]. Prothrombin deficiency is treated with factor replacement in the form of FFP or PCC to a goal prothrombin level of 30% [29].

Factor V Deficiency

FV deficiency is associated with mucocutaneous bleeding and rarely with ICH [30]. There are mild, moderate, and severe deficiency states. Patients with severe deficiency usually present with umbilical stump and mucocutaneous bleeding. Older individuals may present with postoperative bleeding or menorrhagia. FV deficiency is treated with FFP to a goal activity level of 20% to 30%. Alpha granules in platelets contain FV and platelet transfusions have been used in the treatment of FV deficiency when patients have developed neutralizing inhibitors to FV with varying success [31]. Combined deficiency of FV and FVIII should always be considered in the differential diagnosis of patients who present with FV deficiency. This is discussed next [32].

Combined Factor V and VIII Deficiency

Combined FV and FVIII deficiency (F5F8D) is a rare disorder where patients have detectable, but low antigen and activity levels of both factors, typically in the 5% to 15% range. Patients present with increased bleeding following trauma or surgery. Patients are treated with a combination of FFP and FVIII concentrates.

Factor VII Deficiency

Patients with less than 1% FVII activity manifest a severe bleeding disorder, predominantly involving the mucous membranes, muscles, joints, and following surgery or trauma, while those with more than 5% have relatively mild symptoms. Factor VII activity correlates poorly with bleeding severity, but in general, only modest amounts of circulating FVII are required for adequate hemostasis, and bleeding is uncommon, even with surgery, in individuals with FVII activity levels > 15% to 20% [33,34]. In the United States, rFVIIa is used to treat FVII deficiency. Plasma-derived FVII concentrates are available in Europe to treat this disorder [35,36]. When rFVIIa and/or FVII concentrates are unavailable, PCC (depending on factor formulation) or FFP may be used.

Factor X Deficiency

In congenital FX deficiency, severity of bleeding appears to correlate with residual FX activity and may be quite severe. In a case series of Iranian patients with congenital FX deficiency, the most common symptoms were epistaxis, menorrhagia, and hemarthrosis [37]. FX deficiency is treated with PCCs.

Factor XI Deficiency

FXI deficiency, previously known as hemophilia C, is common amongst Ashkenazi Jews where the gene frequency is 8% to 9% [38]. The inheritance is autosomal rather than X linked as with hemophilia A and B. Severe FXI deficiency (< 15% to 20% FXI activity) occurs in homozygotes or compound heterozygotes. Heterozygous individuals have a partial FXI deficiency (20% to 70% FXI activity) [39]. Bleeding is unpredictable as some severe FXI deficiency patients are asymptomatic, while an analysis of 50 kindreds demonstrated that 30% to 50% of heterozygotes experienced significant bleeding [40].

Treatment for FXI deficiency includes FFP, antifibrinolytic agents [41], FXI concentrates (available in the United Kingdom and France) [42], and rFVIIa (not FDA approved for this purpose) [43]. There is concern of a prothrombotic potential associated with FXI concentrates as DIC and arterial thrombosis have been described in up to 10% of patients. Heparin has been added to these concentrates to reduce this thrombotic potential, but there is a general recommendation to maintain FXI levels at no greater than 70 IU per dL [44].

Factor XIII Deficiency

The most common presentation for FXIII-deficient patients is umbilical stump bleeding [45]. FXIII-deficient patients may also experience ICH, hemarthrosis, menorrhagia, and increased bleeding following surgery or trauma [46]. FXIII has a half-life of 8 to 12 days and levels required to maintain hemostasis are only in the range of 2% to 5%. Treatment includes FXIII concentrates, FFP, or cryoprecipitate. Given FXIII's long half-life, factor concentrates may be given once every several weeks as prophylactic therapy [47].

Vitamin K-Dependent Factor Deficiencies

Patients with combined deficiency of the vitamin K-dependent factors (FII, FVII, FIX, FX, proteins C and S) may present with umbilical stump bleeding or ICH [48]. Factor activity levels are variable and generally range from 1% to 30%. High doses of supplemental vitamin K may significantly improve or completely correct deficient factor activities. In acute bleeding episodes, patients may be treated with FFP or PCCs.

Congenital Qualitative Platelet Disorders

Defects in Platelet Adhesion

Bernard–Soulier syndrome (BSS) is a rare, autosomal recessive, severe bleeding disorder characterized by thrombocytopenia, giant platelets, and severe mucocutaneous bleeding [49]. Deficient platelet binding to subendothelial vWF is due to abnormalities (either qualitative or quantitative) in the GP Ib/IX/V complex. The mainstay of treatment in BSS is platelet transfusion during clinically significant hemorrhagic episodes. However, alloimmunization to transfused platelets is often encountered when patients develop neutralizing antibodies to GP Ib/IX/V on transfused platelets which renders those platelets useless. rFVIIa has been used to treat patients with these inhibitors and has proven successful in many cases [50].

Defects in Platelet Aggregation

Glanzmann thrombasthenia is a rare, autosomal recessive disorder characterized by absent platelet aggregation secondary to defective GP IIb/IIIa on the platelet surface. Affected patients present with severe to life-threatening mucocutaneous bleeding. Treatment includes platelet transfusion. However, many patients may become refractory as alloantibodies to transfused platelets form. rFVIIa has been used to treat bleeding in this disorder [51].

Disorders of Platelet Secretion: The Storage Pool Diseases

Platelets contain two types of intracellular granules, alpha and delta (or dense), which are required for an optimal secondary wave of platelet aggregation. The gray platelet syndrome is the most common alpha granule storage pool disease (SPD) and may predispose to early onset myelofibrosis, a

probable consequence of the impaired storage of growth factors such as PDGF [52]. Hermansky–Pudlak syndrome and Chediak–Higashi syndrome are SPDs affecting dense granules. The Hermansky–Pudlak syndrome is associated with oculocutaneous albinism and increased accumulation of an abnormal fat-protein compound, ceroid, in the reticuloendothelial system [53]. The Chediak–Higashi syndrome is characterized by oculocutaneous albinism, neurologic abnormalities, immune deficiency with a tendency to infections, and giant inclusions in the cytoplasm of platelets and leukocytes [54]. The primary treatment for clinically significant bleeding in patients with SPDs is platelet transfusion.

ACQUIRED COAGULATION DISORDERS

Anticoagulant Drugs

Use of anticoagulants in the critical care setting is ubiquitous. The pharmacology, monitoring, and appropriate reversal of anticoagulant drugs are reviewed in detail in Chapter 110.

Generally, patients on anticoagulants who develop clinically insignificant bleeding may be closely monitored while the drug is continued; appropriate therapeutic monitoring (e.g., INR, aPTT, anti-Xa) should also be obtained and followed closely. Major bleeding, except in rare instances, typically should prompt discontinuation of anticoagulant drugs. Consideration should also be given to holding subsequent doses or reducing doses based on laboratory or clinical evolution.

Heparins, Low-Molecular-Weight Heparins, and Fondaparinux

These agents, and management of associated bleeding complications, are discussed in Chapter 110.

Warfarin (Coumadin)

Given its widespread use, warfarin is a common cause of iatrogenic, serious bleeding that frequently requires critical care. Warfarin is an oral vitamin K antagonist that exerts its anticoagulant effects through inhibition of vitamin K-dependent γ carboxylation of the vitamin K-dependent factors (FII, FVII, FIX, and FX). γ carboxylation is required for these coagulation factors to become biologically active. Warfarin also inhibits γ carboxylation of the vitamin K-dependent regulatory proteins C and S. Treatment with warfarin reduces the biologically active levels of all these vitamin K-dependent factors, both pro- and anti-coagulant. However, the net effect at steady state is anticoagulation. Given the half-life of the independent factors affected by warfarin, patients may become relatively prothrombotic in the first several days after warfarin initiation as proteins C and S are the first to become significantly reduced. This is the rationale for "bridging" with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) for the first several days of warfarin administration to abrogate extension of existing thrombosis or development of new ones [55].

Warfarin is monitored via the PT and INR with a typical therapeutic range of 2.0 to 3.0 but this is patient and indication specific [55]. At supratherapeutic doses, the aPTT may also become prolonged.

When asymptomatic, supratherapeutic anticoagulation with warfarin does not generally require treatment beyond reducing the dose or holding warfarin for a period of time to allow for correction in the INR. Consideration may also be given to administering a small dose of vitamin K (1 to 5 mg) which will significantly lower the INR within 24 hours, depending on the INR and clinical scenario. If the patient is experiencing significant or life-threatening bleeding, reversal of anticoagulation is indicated and accomplished by replenishing the vitamin K-dependent factors. This can be achieved using either FFP or PCCs (Table 108.6).

TABLE 108.6

REVERSAL OF WARFARIN-INDUCED ANTICOAGULATION MANAGEMENT OF SUPRATHERAPEUTIC INR

Clinical situation	INR	Actions
No significant bleeding	< 5.0	■ Lower dose, or ■ Hold dose and restart at a lower dose once INR in desired range, or ■ Check INR in 24 h if INR only mildly prolonged
	5.0–9.0	■ Hold warfarin, repeat INR in 24 h ■ Give vitamin K_1 1–2.5 mg PO × 1 if at increased risk of bleeding ■ Check INR in 24 h—when INR in desired range, restart warfarin at adjusted dose
	≥ 9.0	■ Hold warfarin and give vitamin K_1 2.5–5 mg PO × 1 (may repeat in 24 h if INR not improved) ■ When INR in desired range, restart warfarin at adjusted dose
Serious or life-threatening bleeding	Any prolongation in INR due to warfarin administration	■ Hold warfarin ■ Give vitamin K_1 10 mg slow IV push (over 30 min); may repeat in 12–24 h ■ Give FFP, prothrombin complex concentrate (PCC), or rFVIIa for acute reversal ■ Monitor INR and repeat intervention as necessary

Adapted from Ansell J, Hirsh J, Hylek E, et al: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* [6, Suppl]:175s, 2008.

PCCs are plasma-derived products enriched in vitamin K-dependent factors. The typical dose is 25 to 50 U per kg depending on the degree of anticoagulation. There are two types of PCCs available, activated PCC (aPCC) and nonactivated (simply referred to as PCC). The activated form contains activated coagulation proteases that are used in the treatment of hemophilia with inhibitors. The nonactivated formulations were originally licensed for the treatment of hemophilia B, given their high FIX content. Furthermore, there are two types of nonactivated PCCs: 4-factor (FII, FVII, FIX, FX)–containing products and a 3-factor (FII, FIX, FX) product. While the 3-factor product does contain some FVII, it is at a low concentration (less than one-third that of FIX) and therefore is considered a 3-factor concentrate. If a 3-factor concentrate is used for warfarin reversal, rFVIIa may be required as adjunctive treatment to replenish FVII [55]. Notably, only 3-factor PCCs are currently available in the United States; however, a phase III clinical trial is currently enrolling to evaluate the efficacy and safety of a 4-factor PCC in reversal of oral vitamin K antagonist-induced bleeding. Both activated and nonactivated PCCs contain heparin and are therefore contraindicated in patients with heparin-induced thrombocytopenia [56]. As the effects of FFP, PCC, and rFVIIa are transient, 10 mg of parenteral vitamin K (IV over 30 minutes) should also be given to reverse the INR more durably [55]. When available, PCCs are preferred over FFP because they are concentrated into much smaller volumes, can be virally inactivated, and have a lower risk of TRALI (see Chapter 114). The pharmacodynamics of warfarin is discussed further in Chapter 110.

Superwarfarins

The superwarfarins are a group of pharmacologic compounds that are long-acting rat poisons. They have considerably longer half-lives than warfarin (weeks to months versus 1 to 2 days) and are considerably more potent. Superwarfarin poisoning has been associated with homicide and suicide attempts, accidental ingestion, and occupational exposure. Patients typically present with bleeding symptoms and laboratory findings similar to those of warfarin overdose; however, the PT/INR does not appropriately normalize with standard doses of vitamin K. An assay for each of the superwarfarins is necessary to confirm the diagnosis. Patients require high doses of vitamin K for prolonged periods to control bleeding risk. FFP or rFVIIa may be required in episodes of life-threatening bleeding [57].

Direct Thrombin Inhibitors (Argatroban, Lepirudin, Bivalirudin)

Reversal of anticoagulation due to direct thrombin inhibitors (DTIs) in cases of clinically significant bleeding is typically achieved through cessation of drug given a short half-life (< 1 hour). No specific antidote is available and supportive care is the standard. The pharmacodynamics of DTIs are discussed in greater detail in Chapter 110.

Vitamin K Deficiency

Vitamin K deficiency is a frequently encountered problem in hospitalized medical patients. It is particularly common in those with chronic malabsorption syndromes (e.g., cystic fibrosis), malnutrition, and those on broad-spectrum antibiotics [58]. Patients on warfarin and with vitamin K deficiency present with similar laboratory and physical findings, namely prolongation primarily of the PT as well as easy bruising or soft tissue bleeding. Vitamin K deficiency is managed by supplementation of vitamin K. If a patient has a malabsorptive syndrome, parenteral vitamin K is typically recommended.

Since vitamin K-dependent coagulation factors are synthesized in the liver, it can be difficult to distinguish between vitamin K deficiency and a coagulopathy of liver disease (decreased hepatic synthesis of coagulation factors). In clinical scenarios where underlying liver disease is present, it may be beneficial to evaluate coagulation factor levels, both vitamin K-dependent and independent (e.g., FII and FV, respectively). In this example, if both FII and FV levels are decreased, then the patient likely has hepatic synthetic dysfunction. If FV is normal and FII is decreased, then the patient likely has vitamin K deficiency.

Coagulopathy of Liver Disease

An unfortunate hallmark of liver disease is coagulopathy. It stands to reason that since all of the coagulation factors (except FVIII, which is also synthesized in extrahepatic endothelial cells) are made in the liver, end-stage liver disease (ESLD) is marked by multiple coagulation factor deficiencies [59,60]. However, increased extravascular redistribution and increased factor consumption also contribute. The degree of coagulation factor reduction as well as the number of factors reduced typically parallel the severity of liver disease [61]. Factors V and VII appear to be sensitive markers of hepatic synthetic dysfunction with FVII levels typically the most notably affected secondary to its short half-life [62]. A prolongation in the PT is therefore an early marker of liver disease. As hepatic dysfunction progresses and other coagulation factors in the common and contact activation pathway are decreased, the aPTT prolongs. In contrast, FVIII levels are typically elevated in compensated cirrhosis. This may be secondary to an increase in vWF that is seen in cirrhotics [60]. In addition, proteins required for FVIII clearance such as low-density lipoprotein receptor-related protein (LRP) are present in decreased amounts, thus raising FVIII levels. Patients with liver disease may have normal fibrinogen levels, given its long half-life, but they may develop an acquired dysfibrinogenemia associated with abnormal fibrinogen glycosylation that disrupts fibrin polymerization [63,64]. This may be reflected by a normal fibrinogen quantitative assay but an abnormal functional assay such as the TT or RT.

In addition to coagulation factor deficiency, a number of other variables associated with advanced liver disease may contribute to coagulopathy in this population. These include (a) vitamin K deficiency secondary to malnutrition, malabsorption/maldigestion from bile salt insufficiency, and altered intestinal motility [63]; (b) portal hypertension with resultant hypersplenism and secondary thrombocytopenia [65]; (c) decreased thrombopoietin (the principle regulator of platelet production) synthesis by hepatocytes with resultant thrombocytopenia [66]; (d) impaired platelet function as demonstrated by abnormal platelet function, as assessed by PFA-100® [66]; and (e) hyperfibrinolysis secondary to impaired synthesis of plasminogen activator inhibitors and decreased clearance of plasminogen activators (reviewed in reference [67]). Chronic, low-grade DIC may also contribute to coagulopathy (discussed later).

Despite evidence for a significant coagulopathy based on laboratory tests as well as evident petechiae, ecchymosis, purpura, and bleeding after invasive procedures, patients with ESLD rarely bleed spontaneously. It is much more common for them to present with hemorrhage as a result of an underlying anatomic lesion such as from an esophageal varix. There remains active debate as to the actual net degree of coagulopathy in these patients. For instance, Mannucci has argued that defects in platelet number and function may be balanced by increased levels of vWF. Furthermore, decreased levels of

coagulation factors and inhibitors of fibrinolysis are balanced by decreased levels of inhibitors of coagulation and profibrinolytic factors [68]. The end result is a potential rebalancing of hemostasis. The fact that the degree of PT and aPTT prolongation correlates poorly with bleeding after liver biopsy and other potentially hemorrhagic procedures supports this rebalancing notion [69,70]. Ultimately, a more comprehensive assessment of hemostasis is needed as PT and aPTT only assess thrombin generation in a closed system devoid of anticoagulant factors and do not address fibrinolysis at all.

Given that we lack a comprehensive hemostatic assessment tool, many physicians prefer to prophylactically give FFP or other hemostatic agents to patients with ESLD who are to undergo procedures or who have significantly abnormal coagulation laboratory values. Unfortunately, we have little data to support these measures. The current guidelines recommend FFP transfusions only when hemostasis is needed for bleeding or invasive procedures and the PT or aPTT is > 1.5 times normal (reviewed in reference [71]). FFP is generally given at a dose of 10 to 15 mL per kg repeated every 8 hours. Notably, despite repeated infusions of FFP, the PT may not completely correct and therefore clinical response should be monitored rather than relying on the PT as a measure of efficacy [72]. As discussed earlier, patients with ESLD may also develop hypofibrinogenemia or a dysfibrinogenemia. This should be suspected in a patient with a prolonged TT or RT or in a patient who continues to bleed despite FFP infusion. Cryoprecipitate may be required to treat hypo/dysfibrinogenemia as FFP typically does not sufficiently replace fibrinogen. Cryoprecipitate is typically given in doses of 10 pooled units. Patients should be transfused to a goal fibrinogen level of > 100 mg per dL. There are a number of human fibrinogen concentrates available in Europe, and in 2009 the Food and Drug Administration approved the first human fibrinogen concentrate in the United States. It is currently indicated for the treatment of patients with congenital afibrinogenemia and hypofibrinogenemia. Some authors have reported beneficial outcomes in patients given rFVIIa and PCCs in ESLD. However, there are currently no guidelines or randomized trials that address dosing or efficacy [63]. However, given the hypervolemia typical of patients with ESLD, multiple infusions of FFP may not be possible and treatment with PCCs may be considered to reduce volume overload as well as decrease the risk of TRALI. If a 3-factor PCC is used, adjunctive rFVIIa may be indicated [73].

Many have argued for controlled trials to evaluate the role of prophylactic hemostatic agents in this patient population as current practice typically involves using expert opinion and case series data [74].

Disseminated Intravascular Coagulation

DIC is a well-recognized syndrome characterized by both thrombotic and hemorrhagic complications in the setting of a number of defined disorders that are typically associated with systemic inflammation (Table 108.7) [75]. The pathogenesis of DIC is complex and is characterized by widespread activation of the TF coagulation pathway with a marked imbalance between procoagulant and anticoagulant processes resulting in unopposed thrombin generation and diffuse fibrin clot formation with subsequent microvascular occlusion and tissue hypoxia [76]. When severe, these changes may culminate in multiple organ dysfunction syndrome (MODS). The pathogenesis is further reviewed elsewhere [75,77].

The clinical presentation of DIC is variable and the majority of patients do not demonstrate a significant hemorrhagic phenotype [78]. A clinical suspicion for DIC is paramount in establishing its diagnosis. In addition to a compatible underlying condition (e.g., sepsis), abnormal laboratory studies consistent with increased thrombin generation and fibrinolysis (consumptive coagulopathy) are also required. A DIC screening panel is typically composed of PT, aPTT, platelet count, fibrinogen, and D-dimer. DIC is suggested when the laboratories demonstrate increased activation of coagulation (elevated PT/aPTT, decreased fibrinogen) as well as evidence of fibrinolysis (elevated D-dimer or fibrin degradation products). An elevation in PT is a very sensitive measure for DIC but has lower specificity since it may be normal, especially in chronic DIC [79]. Since fibrinogen is an acute phase reactant, it may be normal or even elevated in chronic DIC, thereby limiting its specificity in low-grade DIC. Elevation of D-dimer is a sensitive marker for DIC, in the range of 90% to 100% in one report; however, its specificity limits its utility as a single screening test [80].

The International Society on Thrombosis and Hemostasis established a subcommittee on DIC to develop and validate a scoring system to aid in the diagnosis of DIC. This system is based on platelet count, fibrin degradation products, PT, and fibrinogen level [81]. A prospective validation study demonstrated this scoring system to be 91% sensitive and 97% specific for the diagnosis of DIC, with higher scores correlated with higher 28-day mortality (Table 108.8) [82].

Identification and treatment of the underlying disorder remains the hallmark of treatment for DIC [78]. Treatment of DIC should be based on both the clinical presentation as well as the laboratory results [75]. Recommendations for the management of DIC are based on expert opinion given a lack of published, randomized data. In general, patients who experience

TABLE 108.7

DISORDERS ASSOCIATED WITH DISSEMINATED INTRAVASCULAR COAGULATION

Infection
Gram-negative or Gram-positive septicemia
Rickettsiae—especially Rocky Mountain spotted fever
Spirochetes
Fungi
Viruses—especially herpes
Protozoa—especially malaria
Tissue damage
Trauma
Crush injury
Burn
Heat stroke
Hemolytic transfusion reaction
Neoplasia
Metastatic carcinoma
Leukemia—especially acute promyelocytic leukemia
Chemotherapy
Obstetric disasters
Abruptio placentae
Retained dead fetus
Preeclampsia/eclampsia
Amniotic fluid embolism
Placenta previa, accreta, and percreta
Miscellaneous
Fat embolism
Shock
Cardiac arrest
Giant hemangioma (Kasabach–Merritt syndrome)
Vasculitis
Toxins (snake venom, brown recluse spider bite)
Near drowning—especially fresh water

TABLE 108.8

DIAGNOSTIC SCORE FOR DISSEMINATED INTRAVASCULAR COAGULATION

1. Underlying disorder associated with DIC—if yes → proceed, if no → do not proceed, search for alternative process
2. Obtain global coagulation tests: platelet count, PT, fibrinogen, D-dimer
3. Assign score based on laboratory tests
   a. Platelet count
      i. > 100 = 0, < 100 = 1, < 50 = 2
   b. D-dimer or fibrin degradation products
      i. No increase = 0, moderate increase = 2, strong increase = 3
   c. Prolonged PT
      i. < 3 s = 0, > 3 s but < 6 s = 1, > 6 s = 2
   d. Fibrinogen level
      i. > 1.0 g/L = 0, < 1.0 g/L = 1
4. Calculate score
   a. If ≥ 5, compatible for DIC
   b. If < 5, suggestive, but not confirmed DIC, repeat in 1–2 d

Adapted from Bakhtiara K, Meijers JC, de Jonge E, et al: Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 32(12):2416–2421, 2004.

significant bleeding or who require invasive procedures should be treated with FFP to replace coagulation factors. PCCs may also be considered when hypervolemia complicates FFP administration, but they may lack certain depleted factors such as FV. Furthermore, the literature discusses increased risk for thrombosis given trace amounts of activated factors contained in the preparations [83]. It is unclear if this risk is still present in today's products. Cryoprecipitate should be used to replace fibrinogen if the plasma level is < 100 g per dL. While there is no established threshold at which to transfuse platelets in DIC, in the setting of active bleeding or in anticipation of invasive procedures, platelet transfusions may be indicated.

In contrast to replacing coagulation factors, fibrinogen, and platelets, some investigators have evaluated the role of anticoagulants, namely UFH, in the treatment of DIC. This putative measure is based on the pathologic activation of coagulation-associated with DIC as well as the depletion of endogenous anticoagulants. Initial animal studies evaluating anticoagulants in DIC suggested a benefit [84]; however, subsequent human trials have yielded conflicting results [78,85,86]. To date there are no data from randomized, controlled trials to support the use of UFH in the management of DIC.

More recently, trials of recombinant anticoagulant proteins have been conducted in patients with sepsis-related DIC. Similar to UFH, early trials evaluating tissue factor pathway inhibitor (TFPI) were promising; however, a subsequent phase III trial did not demonstrate survival benefit [87,88]. Large trials evaluating the use of antithrombin concentrates to restore the anticoagulant pathway have also been disappointing [89]. Most recently, considerable attention has been directed toward activated protein C (APC) and sepsis/DIC. Animal models suggest a link between downregulation of the protein C/thrombomodulin system and endotoxin-induced DIC (reviewed in reference [90]). Recombinant human APC (drotrecogin alfa) has been demonstrated to improve mortality and organ function in septic patients. Furthermore, it appears that patients with the most severe sepsis (APACHE score > 25) received the largest benefit [91]. Drotrecogin alfa is not used in DIC unassociated with severe sepsis.

DIC is discussed in further detail in Chapter 109.

Trauma-Induced Coagulopathy

Trauma-induced coagulopathy includes the coagulopathy associated with the stresses of trauma as well as unintended consequences of its treatment. Historically it was felt that the coagulopathy associated with trauma was largely secondary to dilution of the coagulation system with volume and blood replacement. However, it is becoming increasingly apparent that this process is much more dynamic and complicated. Traumatic events requiring massive transfusion of blood lead to significant coagulopathy through a number of mechanisms that include (a) dilution of coagulation proteins and platelets from volume resuscitation, (b) consumptive coagulopathy and thrombocytopenia (through DIC associated with trauma), (c) acidemia which impairs function of the coagulation cascade, (d) hypothermia which impairs function of platelets and coagulation factors, and (e) electrolyte perturbations, particularly hypocalcemia which impairs the calcium-dependent coagulation processes [92]. Prompt attention is required to mitigate the coagulopathy associated with trauma and to rapidly correct it. Clinically, patients have a compatible history of massive trauma requiring aggressive resuscitation and typically have a prolongation of PT and aPTT that corrects on mixing study, as well as thrombocytopenia and often hypofibrinogenemia. Treatment is targeted at correcting or preventing the occurrence of the above listed mechanisms that have been associated with the development of trauma induced coagulopathy. Most guidelines recommend transfusion of red blood cells to a target hemoglobin of 7 to 10 g per dL to maintain rheology, FFP administration to a goal PT/aPTT of < 1.5 × upper limit of normal, platelet transfusion to keep platelets > 50×10^9/L (or > 100×10^9 in patients with brain injury), and fibrinogen > 100 mg per dL [93,94]. Notably, recent large animal models of dilutional coagulopathy suggest that treatment with PCC was as effective as FFP in correcting coagulopathy and warranted further investigation [95]. Some studies also suggest that rFVIIa may be beneficial (reviewed in reference [96]).

Acquired Hemophilia A

The most common antibodies that affect clotting factor activity with a resultant hemorrhagic phenotype are directed against FVIII. Acquired hemophilia A, or acquired FVIII deficiency, is a rare disorder with an estimated incidence of 1.0 per million that is caused by autoantibodies directed against a patient's endogenous FVIII, resulting in low FVIII activity levels [97]. Acquired hemophilia A is most commonly an idiopathic condition that occurs in the elderly but can also be associated with malignancy, drugs, autoimmune disorders, and the postpartum state.

Acquired hemophilia should be suspected in patients without a prior bleeding history who present later in life with significant, large ecchymoses, hematomas, mucosal, gastrointestinal bleeding, or who experience significant bleeding following surgery or trauma. Hemarthroses that are a hallmark of congenital hemophilia are not typical of acquired hemophilia.

Patients with acquired hemophilia present with bleeding symptoms and a prolonged aPTT in contrast to patients with a lupus anticoagulant who typically present with a prolonged aPTT and thrombotic complications [97]. Once acquired hemophilia is suspected based on clinical presentation and a prolonged aPTT, an incubated aPTT mixing study should be performed. Since FVIII inhibitors are commonly time and temperature dependent, the mixing study should be performed

at 37°C for 1 to 2 hours. In the case of an acquired FVIII inhibitor, the incubated aPTT will not completely correct into the normal range which indicates the presence of an inhibitor. A FVIII activity level may also be helpful to identify the inhibitor as FVIII specific. The strength of the inhibitor may be quantified in a Bethesda assay. The strength of the inhibitor has treatment implications.

Treatment goals of these patients are twofold: (a) control of bleeding and (b) eradication of the inhibitor. Bleeding in patients with low-titer inhibitors (< 5 BU) can often be treated with high doses of FVIII concentrates [98]. Bleeding in patients with high-titer inhibitors is treated with a FVIII inhibitor bypassing agent, such as an aPCC or rFVIIa [99]. Porcine FVIII was also an option for patients with a low-titer inhibitor since the inhibitor titer to porcine FVIII is only 5% to 10% of the titer against human FVIII [100]. Unfortunately, this product was removed from production in 2004 given concerns for porcine parvovirus contamination. Clinical trials are currently underway evaluating recombinant porcine FVIII. Inhibitor eradication typically involves immunosuppression, though spontaneous resolution of the inhibitor can occur [98]. There is an unfortunate relapse rate of approximately 20%; however, 70% of these patients can be brought back into a second remission [101].

ACQUIRED PLATELET DISORDERS/DYSFUNCTION

Medications

The antiplatelet effect of medications is the most common cause for acquired platelet dysfunction. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications that affect platelet function (Table 108.9) [102]. Their predominant antiplatelet effect is achieved through the inhibition of platelet cyclooxygenase (COX-1) which in turn ultimately inhibits vasoconstriction and platelet aggregation [103]. Inhibition of COX-1 by aspirin is irreversible for the life of the platelet and is dose-dependent. There is an increased risk of bleeding in patients taking aspirin, and two recent meta-analyses have described an approximate 1% increase in absolute risk of bleeding in patients taking aspirin compared to placebo [104,105]. Notably, this bleeding risk does not appear to be dose dependent when the total daily dose is ≤325 mg per day but does increase with concomitant administration of other anticoagulants or antiplatelet agents [106,107]. The primary site of bleeding associated with aspirin is gastrointestinal. NSAIDs, on the other hand, reversibly inhibit COX-1 for the length of time that the medication remains metabolically active. Platelet function is not affected by the newer COX-2 specific inhibitors or acetaminophen.

Dipyridamole is a less frequently used antiplatelet drug with an unclear mechanism of action. It has historically been used for stroke prophylaxis. There does not appear to be a significant increase in bleeding risk for patients taking dipyridamole versus placebo in several randomized trials evaluating the efficacy of dipyridamole in stroke prevention [108].

Clopidogrel (Plavix) belongs to a class of antiplatelet agents known as the thienopyridines and is being used with increasing frequency in the treatment of cardio- and cerebrovascular disease. Thienopyridines are irreversible antagonists to the platelet P2Y12 receptor which inhibits ADP-mediated platelet aggregation. The thienopyridines, particularly ticlopidine (Ticlid), have been implicated in the development of thrombotic thrombocytopenic purpura (TTP) [109].

The GP IIb/IIIa antagonists are a group of antiplatelet agents that are primarily used during coronary procedures. These drugs impair aggregation by inhibiting the cross bridging of platelets by fibrinogen. This class is associated with an increased risk of bleeding, particularly at the puncture site for percutaneous coronary intervention. There does not appear to be an increased risk for intracerebral hemorrhage for patients receiving GP IIb/IIIa inhibitors versus heparin [110]. These agents are also associated with thrombocytopenia, often profound, that may result in significant bleeding complications [111].

Many other medications including large doses of penicillins, psychotropic drugs such as fluoxetine, dietary supplements such as fish oil, gingko, garlic, and cumin may impair platelet function, although not typically to a significant degree [102].

Laboratory testing to confirm an acquired platelet defect secondary to medication is rarely necessary as clinical history and medication record usually suffice. However, if needed for confirmation, platelet function testing may be useful. Treatment for drug-induced platelet dysfunction depends on the severity of bleeding as well as the medication involved. In most cases, minor bleeding may be addressed by withholding the medication. In more severe cases, platelet transfusion may be indicated depending on timing of the last dose as well as its specific platelet effect. In general, platelets have a life span on average of 7 to 10 days. As a result, the bone marrow replaces approximately 10% of the body's platelets each day. Therefore, if a medication irreversibly inhibits platelet function, platelet transfusion may be needed to reverse the antiplatelet effect until the bone marrow has sufficiently replenished the affected platelets. For most situations, a single platelet transfusion is sufficient to correct bleeding association with disordered platelets.

Acquired platelet dysfunction due to antiplatelet agents is discussed in further detail in Chapter 109.

TABLE 108.9

DRUGS THAT COMMONLY AFFECT PLATELET FUNCTION

- Analgesics
  - Aspirin
  - NSAIDs
- Cardiovascular medications
  - Dipyridamole
- P2Y12 receptor blockers—thienopyridines
  - Ticlid (ticlopidine)
  - Plavix (clopidogrel)
  - Effient (prasugrel)
- GP IIb/IIIa inhibitors
  - ReoPro (abciximab)
  - Aggrastat (tirofiban)
  - Integrilin (eptifibatide)
- Antibiotics
  - β-Lactam antibiotics—e.g., PCN, cephalosporins
- Psychotropic
  - Antidepressants (fluoxetine)
  - Phenothiazines
- Herbal supplements
  - Fish oil
  - Cumin
  - Garlic
  - *Ginkgo biloba*
  - Turmeric

Uremia

The multisystem organ dysfunction encountered in critically ill patients often includes acute kidney injury and subsequent uremia. Bleeding associated with uremia has long been recognized

and has historically been associated with a prolonged bleeding time. However, the degree of BT prolongation neither correlates with the degree of azotemia nor the severity of bleeding symptoms. The clinical manifestations of uremic bleeding are predominantly mucocutaneous though patients may present with epistaxis, gastrointestinal bleeding, hematuria, or increased bleeding following surgery or procedures [112].

Despite this long-recognized association between uremia and a bleeding diathesis, the exact pathophysiology remains poorly defined though impairment in platelet function appears integral [113]. There are data to suggest that this is a multifactorial process and includes an acquired platelet defect as well as impairment in platelet–endothelium interaction. Additional factors include vWF abnormalities, anemia which affects rheology, thrombocytopenia, uremic toxins, and increased nitrous oxide (NO) production [114]. The presence of a uremic toxin is supported by the improvement in platelet function in patients following dialysis. Notably, urea is unlikely to be the primary toxin as there is no positive correlation between blood urea nitrogen and bleeding risk [115]. NO is produced by endothelial cells and platelets and inhibits platelet aggregation. Plasma from uremic patients has increased NO and the addition of an NO synthesis inhibitor to uremic rats improved BT [116,117].

Treatment for uremic bleeding often includes aggressive dialysis which may correct the bleeding and has been suggested to prevent uremic bleeding. DDAVP has been recommended as the first-line therapy for uremic bleeding (2 to 4 μg per kg intranasally or 0.3 μg per kg by slow intravenous infusion); it improves platelet function in uremia, most likely due to release of FVIII and vWF [118]. If no improvement is noted after the first dose, further doses should not be given. If DDAVP is ineffective or contraindicated, cryoprecipitate may be given (10 units every 12 to 14 hours). Improvement in bleeding in response to cryoprecipitate is likely related to FVIII and vWF [119]. Correction of anemia to a goal hematocrit of 30% corrects the BT in many patients through improved rheology. This may be accomplished via red cell transfusions in the acute period or erythropoietin over prolonged periods. Erythropoietin may also have beneficial effects on platelet function [120]. Conjugated estrogens may improve uremic bleeding and appears to do so in a dose-dependent manner presumably by reducing NO production [121,122] (reviewed in reference [123]).

Hematologic Disorders

Abnormal platelet function is frequently noted in patients with a number of primary hematologic disorders, including myelodysplastic syndromes and myeloproliferative disorders. The bleeding diathesis occurs out of proportion to what would be expected in patients with similar quantitative platelet defects. In general, the mechanisms underlying the platelet dysfunction seen in these disorders are poorly understood but probably reflect the genetic and developmental abnormalities in stem cells that underlie these disorders. The severity of the predisposition to bleeding cannot be reliably predicted from the results of the bleeding time, platelet count, or in vitro platelet function tests.

The bleeding complications of the myeloproliferative disorders have been estimated in the literature to range from 1.7% to 37%, depending on the disorder and population screened [124]. The bleeding manifestations in both polycythemia vera (PV) and essential thrombocythemia (ET) involve the skin and mucous membranes and include menorrhagia, epistaxis, ecchymosis, and gastrointestinal bleeding. This pattern of bleeding suggests an underlying platelet or vWD defect. It has long been assumed that dysfunctional platelets derived from abnormal stem cells were responsible for increased bleeding with these disorders. Recently, however, there are increasing data to suggest that extreme thrombocytosis may paradoxically result in an acquired type 2 vWD which contributes to the bleeding diathesis [125]. Other conditions associated with acquired vWD include Heyde's syndrome, which is the association of tight aortic stenosis with gastrointestinal arteriovenous malformations. In this condition, the shear stress associated with the stenotic aortic valve consumes the high-molecular-weight multimers of vWF [126].

Treatment of the underlying disorder remains the mainstay though platelet transfusions may be needed for clinically significant bleeding. If acquired vWD is suspected, it should be confirmed through appropriate testing (to be discussed later) prior to initiating directed treatment. Treatment depends largely on the degree of defect and could include intravenous immune globulin, DDAVP, or vWF replacement [125].

OTHER ACQUIRED BLEEDING DISORDERS

Acquired vWD

Acquired vWD is a heterogenous disorder that is associated with a number of different disease states. Several distinct pathophysiological mechanisms are involved which include increased vWF clearance or proteolysis, vWF adsorption to cells with subsequent increased clearance, decreased synthesis, and antibody formation against vWF [127]. Lymphoproliferative and autoimmune disorders are most commonly associated with acquired vWD.

In general, mechanisms underlying acquired vWD are divided into immune- and nonimmune-mediated categories. Immune-mediated acquired vWD is suggested by mixing studies which show an inhibition of vWF in a functional assay. Proposed nonimmune mechanisms include (a) vWF being adsorbed onto cells (e.g., Wilm's tumor, platelets in myeloproliferative disorders, plasma cells in multiple myeloma, and Waldenström's macroglobulinemia), (b) increased proteolysis of HMW multimers at sites of high blood shear flow rates in patients with aortic stenosis, angiodysplasia, and congenital heart disease, (c) decreased synthesis in hypothyroidism, and (d) proteolysis by plasmin during increased periods of fibrinolysis such as with thrombolytic therapy and DIC. A diagnosis should be expected if a patient has a bleeding phenotype similar to a patient with vWD, a compatible underlying disorder, an absence of lifelong bleeding symptoms, and a negative family history [128]. Treatment for acquired vWD is aimed at correcting the underlying disorder if possible and while promoting hemostasis as one would in patients with congenital vWD (e.g., DDAVP, factor concentrates, antifibrinolytics).

Acquired FII (Prothrombin) Inhibitors

Clinically, patients with antiphospholipid antibodies most commonly have a thrombotic phenotype; however, rarely these patients may also have an antibody directed against prothrombin. This antibody binds to prothrombin and increases its clearance, which results in low FII activity levels and clinically significant bleeding. This disorder should be considered in a bleeding patient with evidence for prolongation in PT and PTT. The PT should correct with mixing, the PTT will not. Tests for the lupus inhibitor will be positive, and measurements of FII activity as well as FII antigen will be low. Treatment for acute hemorrhage involves FFP, typically at a dose of 15 to 20 mL per kg with a goal FII activity of > 30% [129]. PCCs may also be used.

Acquired FV Inhibitors

Acquired FV inhibitors are noted to occasionally occur following cardiac surgery after exposure to topical thrombin or fibrin-glue preparations. These preparations may be contaminated with bovine FV and antibodies may form which cross-react with human FV. A recent retrospective analysis of acquired FV patients noted that 68% of patients presented with bleeding events that most commonly manifested as mucocutaneous events [130]. Patients typically present with a significant prolongation in both the PT and PTT. This prolongation fails to correct in a mixing study. Inhibitor specificity to FV is demonstrated with a low FV activity. FFP is not recommended as a treatment since FV is present in such a low concentration that it is quickly neutralized by the inhibitor. PCCs are likewise felt to be unhelpful given their low FV content. Plasma exchange and platelet transfusions have been used successfully to control bleeding. It is thought that FV contained in the alpha granules of circulating platelets is protected from inhibition until the platelet becomes activated at the site of vessel damage. More recently, rFVIIa has been reported to successfully promote hemostasis in a small case series [131].

Acquired FX Deficiency

Acquired FX deficiency is associated with amyloidosis. It is thought that amyloid fibrils bind to FX and thereby remove it from circulation. Treatment of the underlying amyloidosis and/or splenectomy has been shown to improve the circulating FX level [132]. PCCs are the preferred treatment for acute bleeding episodes.

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CHAPTER 109 ■ THROMBOCYTOPENIA

THOMAS G. DELOUGHERY

Thrombocytopenia is common in the intensive care unit (ICU). Platelet counts below 100,000 per μL occur in 25% to 38% of ICU patients and counts fewer than 10,000 per μL occur in 2% to 3% [1–4]. A variety of disease processes can lead to thrombocytopenia, ranging from an epiphenomenon of the illnesses that lead to the ICU admission to a devastating complication of therapy (Table 109.1).

The immediate priorities in thrombocytopenic patients are to establish the validity and severity of the thrombocytopenia, evaluate for life-threatening processes such as heparin-induced thrombocytopenia or thrombotic thrombocytopenic purpura, and initiate therapy. In the critical care setting, therapeutic decisions often have to be made before a definitive cause of the thrombocytopenia is established.

INITIAL EVALUATION

The initial assessment should be rapid, focusing on whether the patient is bleeding or experiencing thrombosis; the underlying disorder(s) leading to ICU admission; current medications; and (if available) past medical history.

In the assessment of bleeding, one should detect whether the patient is suffering from "structural" aberrancies (e.g., bleeding from a gastric ulcer) or generalized bleeding, which may suggest a hemostatic defect such as may occur due to thrombocytopenia. One should inspect sites of instrumentation, such as IV sites or chest tube drainage, and the mucosa for bleeding. The fingertips and toes should be examined for evidence of emboli or ischemia.

TABLE 109.1

DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA

Disseminated intravascular coagulation
Drug-induced thrombocytopenia
HELLP syndrome
Hemophagocytic syndrome
Heparin-induced thrombocytopenia
Liver disease
Posttransfusion purpura
Pseudothrombocytopenia
Thrombotic thrombocytopenia purpura

HELLP, hemolysis, elevated liver tests, and low platelets.

TABLE 109.2

LABORATORY TESTS IN EVALUATION OF THROMBOCYTOPENIA

Prothrombin time/INR Activated partial thromboplastin time D-dimer LDH Creatinine Bun Peripheral smear
LDH, lactate dehydrogenase level.

Exposure to medicines is a common cause of thrombocytopenia [5,6]. One should carefully review the record of current and recently administered medications and ask the patient (if possible) and family about medications (prescribed, over the counter, and herbal) [7,8] that the patient has recently taken.

Laboratory Testing

In the patient with thrombocytopenia, examination of the blood smear can quickly reveal whether pseudothrombocytopenia (artifactual platelet clumping) [9] is present and verify the degree of thrombocytopenia (Table 109.2). Although exceptions do exist, the magnitude of thrombocytopenia can be an aid in the differential diagnosis of low platelet counts (Table 109.3). Heparin-induced thrombocytopenia and thrombotic microangiopathy (including thrombotic thrombocytopenic purpura, TTP) often present with modest thrombocytopenia (50 to 100 × 10^9 per L). The smear should be carefully reviewed for presence of fragmented red cells (schistocytes). Laboratory assessment of liver function and renal function also should be assessed. A markedly elevated level of lactate dehydrogenase level (LDH) out of proportion to other liver function abnormalities characteristically occurs in TTP and hantavirus infection [10,11]. If there is any suspicion of HIT, all heparin should be stopped and alternative antithrombotic agents should be started [12,13]. Assessment of platelet function can be difficult and must be based largely on clinical judgment. The bleeding time or the platelet function assay (PFA) is rarely useful in the evaluation of a thrombocytopenic patient, because the low platelet count leads to prolongations in the test endpoint [14].

TABLE 109.3

TYPICAL PLATELET COUNTS IN VARIOUS DISEASE STATES

Moderate thrombocytopenia (50–100,000 per μL) Thrombotic thrombocytopenic purpura Heparin-induced thrombocytopenia Disseminated intravascular coagulation Hemophagocytic syndrome
Severe thrombocytopenia (< 20,000 per μL) Drug-induced thrombocytopenia Posttransfusion purpura Immune thrombocytopenia

Diagnostic Clues

The reason for the ICU admission is a very important indicator in evaluation of thrombocytopenia (Table 109.4) [15]. For example, thrombocytopenia in patients who present with sudden-onset multiorgan system failure may indicate TTP or sepsis. In long-term critical care patients, new-onset thrombocytopenia may be a manifestation of HIT, drug-induced thrombocytopenia, occult or established sepsis, or bacteremia [16].

IMMEDIATE THERAPY—PLATELET TRANSFUSION

Although platelet thresholds below which critically ill patients are at risk for severe bleeding are likely to vary among patients, clinical practice generally dictates that a platelet count above 10,000 per μL does not require platelet transfusion, as long as the patient is stable without signs of bleeding, is not receiving platelet inhibitors, has preserved renal function, does not require an invasive procedure, and does not have aggressive DIC [17]. If any of these is present, especially major or life-threatening hemorrhage (such as intracranial), then a threshold of greater than 50,000 per μL is reasonable [18,19]. An exception is thrombocytopenia due to thrombotic microangiopathy (TTP), wherein platelet transfusion is contraindicated unless perhaps the platelets are transfused slowly and plasma exchange already is underway. Platelet transfusions should comprise six to eight platelet concentrates or one single-donor plateletpheresis unit. Additional discussion regarding transfusion of blood products in critically ill patients is found in Chapter 114.

THROMBOCYTOPENIA

Heparin-Induced Thrombocytopenia

HIT occurs due to the formation of antibodies directed against the complex of heparin and platelet factor 4 [12,20]. This complex in a minority of cases binds to the Fcγ RIIA receptor, activating platelets and macrophages. The frequency of HIT is 1% to 5% when unfractionated heparin is used but less than 1% with low-molecular-weight heparin [21]. HIT is more common in women and more common in surgery patients than medical patients [22].

HIT should be suspected when there is a sudden onset of thrombocytopenia with either at least a 50% drop in the platelet count from baseline or the platelet count falling to less than 100 × 10^9/L in a patient receiving heparin in *any* form. HIT usually occurs at least 4 days after starting heparin but may occur suddenly in patients with recent (less than 3 months) exposure [23]. An often overlooked feature of HIT is recurrent thrombosis in a patient receiving heparin despite a normal platelet count [24]. Recently, a scoring system—the four Ts—has been validated in several critical care studies as a means of assessing the pretest probability of HIT [25,26] (Table 109.5).

Patients with very low scores are very unlikely to have HIT and can forgo PF4-heparin antibody testing and empiric therapy. A biphasic pattern of thrombocytopenia following cardiac surgery—namely, recovery from the postsurgical thrombocytopenia followed by recurrent thrombocytopenia—is strongly predictive for HIT [27].

The diagnosis of HIT can be challenging in the critical care patient who has multiple reasons for being thrombocytopenic.

TABLE 109.4

DIAGNOSTIC CLUES TO THROMBOCYTOPENIA

Clinical setting	Differential diagnosis
Cardiac surgery	Cardiopulmonary bypass, HIT, dilutional thrombocytopenia, TTP
Interventional cardiac procedure	Abciximab or other IIb/IIIa blockers, HIT
Sepsis syndrome	DIC, ehrlichiosis, sepsis hemophagocytic syndrome, drug-induced, misdiagnosed TTP, mechanical ventilation, pulmonary artery catheters
Pulmonary failure	DIC, H1N1, infection hantavirus pulmonary syndrome, mechanical ventilation, pulmonary artery catheters
Mental status changes/ seizures	TTP, ehrlichiosis
Renal failure	TTP, dengue, HIT, DIC
Cardiac failure	HIT, drug-induced, pulmonary artery catheter
Postsurgery	Dilutional, drug-induced, HIT, TTP
Pregnancy	HELLP syndrome, fatty liver of pregnancy, TTP/HUS
Acute liver failure	Splenic sequestration, HIT, drug-induced, DIC

DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver function tests, and low platelets; HIT, heparin-induced thrombocytopenia; TTP, thrombotic thrombocytopenic purpura.

In this situation, the laboratory assay for HIT may be helpful. Two levels of HIT testing exist. Increasingly, an ELISA assay that detects the presumed pathogenic antiheparin-platelet factor 4 antibodies is evaluated initially [13]. This test is very sensitive but in some populations not specific. For example, 25% to 50% of cardiac surgery patients will show positive results (presumably due to platelet activation in the bypass circuit) [28,29]. A negative test rules out HIT in all but the highest-risk patients.

A second type of test, a (functional) platelet aggregation assay, such as the serotonin release assay, comprises patient plasma, donor platelets, and heparin. If added heparin induces platelet aggregation, the test is considered to be positive. The test is technically demanding, but if performed carefully can be sensitive and specific [12,13,30]. One caveat is that early in the HIT disease process, the test can be negative but then turns positive 24 hours later as the antibody titer increases. Due to substantial frequency of false positivity of PF4-heparin ELISA among cardiovascular, dialysis, and vascular surgery patients, a diagnosis of HIT should be confirmed by a serotonin release assay, even if treatment for HIT already has been initiated.

The first step in therapy of HIT consists of stopping *all* heparin. Low-molecular-weight heparins cross-react with the HIT antibodies and therefore these agents are also contraindicated. Institution of warfarin therapy alone following a diagnosis of HIT has been associated with an increased risk of thromboses and is also contraindicated. Due to the high risk of thrombosis (53% in one study) [21] among HIT patients, antithrombotic therapy should be administered to all patients [12]. For immediate therapy of HIT patients, several antithrombotic agents are available [12,20,31] (Table 109.6).

Argatroban is a synthetic thrombin inhibitor with a short half-life of 40 to 50 minutes [12,32]. Dosing is 2 µg per kg per minute with the infusion adjusted to keep the aPTT 1.5 to 3 times normal. One advantage of argatroban is that it is not renally excreted and no dose adjustment is necessary in renal disease [33]. These characteristics make it the most useful agent for patients in the critical care unit. However, argatroban

TABLE 109.5

PREDICTION RULE FOR HEPARIN-INDUCED THROMBOCYTOPENIA

Points	2	1	0
Thrombocytopenia	> 50% fall from baseline and nadir 20–100 × 10^9/L	30%–50% fall or nadir 10–19 × 10^9/L	Fall < 30% or nadir < 10 × 10^9/L
Timing of platelet fall	Onset day 5–10 of heparin or < 1 d if patient recently exposed to heparin	Consistent but not clear records or count falls after day 10	Platelets fall < 5 d and no recent (100 d) heparin
Thrombosis	New thrombosis or skin necrosis or systemic reaction with heparin	Progressive or recurrent thrombosis or suspected but not proven thrombosis	None
Other cause for thrombocytopenia	None	Possible	Definite

Notes: Patients with a low probability score are very unlikely to have HIT and can forgo PF4-heparin antibody testing and empiric therapy. Patients with intermediate and high scores should receive empiric therapy until definitive testing can be obtained.
Total score: 6–8, high probability; 4–5, intermediate probability; 0–3, low probability.
Adapted from Lo et al. [25] and Crowther et al. [26].

TABLE 109.6

TREATMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA

Argatroban
Therapy: initial dose of 2 μg/kg/min adjusted to an aPTT of 1.5–3.0 times normal
Reversal: no antidote but $T_{1/2}$ □ 40 min
In severe liver disease (jaundice) dose at 0.5 μg/kg/min adjusted to an aPTT 1.5–3.0 times normal
For patients with multiorgan system failure: 1 μg/kg/min adjusted to aPTT 1.5–3.0 times normal
Post-CABG—0.5–1 μg/kg/min adjusted to aPTT 1.5–3.0 times normal
Indication: prevention and treatment of thrombosis in HIT

Bivalirudin
Bolus: 1 mg/kg
Infusion: 2.5 mg/kg/h for 4 h and then 0.2 mg/kg/h for 14–20 h
Renal adjustment:
For creatinine clearance of 30–59 mL/min, decrease dose by 20%
For creatinine clearance of 10–29 mL/min, decrease dose by 60%
For creatinine clearances less than 10 mg/min, decrease dose by 90%
Note: Antilepirudin antibodies may cross-react with bivalirudin
Indication: Percutaneous coronary intervention, in patients with or without HIT

Lepirudin
Therapy: VERY sensitive to renal function—half-life can go from less than an hour to over 100 h in renal failure. Not recommended in renal insufficiency. May be used in hepatic failure.
- Initial IV bolus 0.4 mg/kg IV push (may be omitted or reduced to 0.2 mg/kg, unless there is life- or limb-threatening thrombosis):
- Continuous infusion: initial rate determined by renal function:
  - GFR > 60 mL/min: 0.10 mg/kg/h
  - GFR 45–60 mL/min: 0.075 mg/kg/h
  - GFR < 45 mL/min: lepirudin not recommended (consider argatroban)
- Perform aPTT at 4-h intervals until steady state within the therapeutic range (1.5–2.0 times patient baseline aPTT) is achieved

Notes: Antilepirudin antibodies form in 60%–80% of patients on lepirudin and can prolong lepirudin effect. Rare patients may have fatal anaphylaxis.
Indication: Prevention and treatment of thrombosis in HIT

Fondaparinux[a]
Therapy: 7.5 mg every 24 h (consider 5.0 mg in patients under 50 kg and 10 mg in patients over 100 kg)
Reversal: protamine ineffective; see Chapter 110: Antithrombotic Therapy.

[a]Fondaparinux is not approved for treatment of HIT. Its use, however, may be considered after initial anticoagulation with a direct thrombin inhibitor has been administered and the platelet count has recovered, while awaiting a therapeutic INR from therapy with warfarin.
Adapted from Laposata et al. [31], Kondo et al. [32], Hyers et al. [212], Hirsh et al. [213], Hirsh et al. [214].

must be used with caution in patients with severe liver disease by using an initial dose of 0.5 μg per kg per minute [32]. Also metabolism appears to be decreased in patients with multiorgan system failure and these patients should receive a dose of 1 μg per kg [34]. Argatroban (like all thrombin inhibitors) prolongs the prothrombin time/INR (PT/INR) making initiation of warfarin therapy difficult. If available, the chromogenic Xa assay can be used to adjust warfarin therapy [35]. Also, if the patient is on a drip of 2 μg per kg per minute or less, one can simply aim for a PT/INR of more than 4.0 as therapeutic. Unfortunately, there is no agent that can reverse argatroban.

Lepirudin, another direct inhibitor of thrombin, is also monitored using the aPTT. The half-life of lepirudin is short, but the drug accumulates in renal insufficiency with the half-life increasing to more than 50 to 100 hours. Recent data indicate that a lower dosing regimen that is recommended on the package insert may result in lower bleeding rates [12]. There is no antidote for lepirudin. Patients with even slight renal insufficiency (creatinine greater than 1.5) must have their lepirudin doses adjusted to avoid overanticoagulation [36]. Up to 80% of patients receiving long-term lepirudin therapy will develop antibodies that reduce the metabolism of hirudin and *increase* the therapeutic effect of lepirudin [37,38]. Patients on long-term (> 6 days) lepirudin therapy should still continue to have monitoring to avoid overanticoagulation.

Bivalirudin is a semisynthetic direct thrombin inhibitor. Its indication involves patients undergoing percutaneous coronary intervention, but other patients may receive it as a treatment for HIT.

The indirect anti-Xa inhibitor fondaparinux does not cross-react with HIT antibodies [12,39], suggesting a potential role in therapy of HIT [40]. However, it has not been studied as extensively in HIT as have the DTIs. Additionally, exposure to fondaparinux has been rarely associated with a syndrome similar to delayed-onset HIT [41]. In the future, newer agents such as dabigatran and rivaroxaban may be suitable for management of patients with HIT.

The issue of platelet transfusion remains controversial [42]. Patients with HIT rarely bleed, which reduces clinical concern over the potential for platelet transfusions, but a prudent

approach would be to reserve transfusion of platelets for the rare patient with severe thrombocytopenia who also has life-threatening bleeding.

As mentioned earlier, initiation of warfarin as the sole antithrombotic agent in the initial treatment of HIT has been associated with limb gangrene. In patients receiving a direct thrombin inhibitor, warfarin can be started in small doses (2 to 5 mg daily) once the platelet count has recovered. These often malnourished patients tend to have a dramatic response to warfarin therapy and excessive anticoagulation can easily occur. One should overlap warfarin and parental therapy by 2 to 3 days as there is evidence that patients may do worse if therapy with a DTI is truncated [32].

Patients with HIT should be carefully screened for any thrombosis, at least by performing lower extremity Doppler ultrasound. If thrombosis is present, at least 3 months of therapeutic anticoagulation are required, whereas HIT without thrombosis usually is treated with 30 days of therapeutic anticoagulation.

Thrombotic Thrombocytopenic Purpura

TTP should be suspected when any patient presents with thrombocytopenia and microangiopathic hemolytic anemia (as evidenced by schistocytes on the blood smear and biochemical evidence of hemolysis); end-organ damage, mostly manifesting as renal insufficiency or neurologic phenomena, and fever also may occur, although the minority of patients with TTP present with all of the aforementioned features [43–45]. Critical care patients with TTP most often present with intractable seizures, strokes, or sequela of renal insufficiency. Postsurgical TTP may occur 1 to 2 weeks after major surgery, and is heralded by decreasing platelet counts and renal insufficiency [46]. Many patients who present to the critical care unit with TTP have been misdiagnosed as having sepsis, "lupus flare," or vasculitis.

Evidence is strong that many patients with the classic form of TTP have an inhibitor against an enzyme that is responsible for cleaving newly synthesized von Willebrand factor (vWF) [45,47,48]. vWF is synthesized as an ultra large multimer that can spontaneously aggregate platelets. The enzyme, ADAMTS13, cleaves vWF into a smaller form that can circulate [48,49]. Presumably when ADAMTS13 is inhibited in TTP, the ultra large multimers can spontaneously aggregate platelets leading to the clinical syndrome of TTP. However, many patients with classic TTP have normal activity of ADAMTS13 and reduced levels are found in other diseases implying other factors are important in pathogenesis of TTP [50–52].

There is currently not a single diagnostic test for TTP but rather the diagnosis is based on the clinical presentation [43,45]. Patients uniformly will have a microangiopathic hemolytic anemia with the presence of schistocytes on the peripheral smear. Renal insufficiency and not frank renal failure is the most common renal manifestation. Thrombocytopenia may range from a mild decrease in platelet number to platelets being undetectable. The findings of thrombocytopenia with a relative normal prothrombin time help eliminate DIC from the differential [53]. The LDH is often extremely elevated and is a prognostic factor in TTP [54]. Finding very low levels of ADAMTS13 due to an inhibitor may also be a negative prognostic factor [55]. However, lack of standardization and slow turnaround time still make this assay difficult to use clinically.

Untreated TTP is rapidly fatal. Mortality in the preplasma exchange era ranged from 95% to 100%. Today plasma exchange therapy is the cornerstone of TTP treatment and has reduced mortality to less than 20% [11,43,56–58].

Glucocorticoid therapy, either 1 to 2 mg per kg of methylprednisolone until remission or 1 g of methylprednisolone initially, may be given to patents presumed to have TTP, although this intervention is not practiced in all centers [45]. The glucocorticoid may be continued until the patient has fully recovered and perhaps longer, given the presumed autoimmune nature of the disease and the high relapse rates. Plasma infusion is beneficial but [47] plasma exchange has been shown to be superior to simple plasma infusion in therapy of TTP [56]. This may be due to the ability of plasma exchange to give very large volumes of fresh frozen plasma and removal of inhibitory antibodies. In patients who cannot be immediately exchanged, plasma infusions should be started at a dose of one unit every 4 hours. Patients with all but the mildest cases of TTP should receive 1 to 1.5 plasma volume exchange each day for at least 5 days [43]. Daily plasma exchange should be continued daily until the LDH has normalized, at which point the frequency of exchange may be taped, starting with every-other-day exchange. If the platelet count falls or LDH level rises, daily exchange should be reinstated [59]. Since the platelet count can be affected by a variety of external influences, the LDH level tends to be the most reliable marker of disease activity [60]. There is increasing evidence that the use of the anti-CD20 therapy may reduce the incidence of relapses and shorten the duration of therapy in refractory disease [48].

Renal insufficiency should be managed in the typical fashion. About 50% of patients require renal replacement therapy.

Hemolytic Uremic Syndrome

Classically, hemolytic uremic syndrome (HUS) comprises the triad of renal failure, microangiopathic anemia, and thrombocytopenia [61,62]. Two major forms are recognized: a "typical" form, which occurs in young children with an antecedent diarrheal illness, and an "atypical" form.

Typical HUS

Typical HUS (also referred to as HUS D+) occurs typically in children under the age of 4, although cases in adolescents and adults may occur. Children often have a prodrome of diarrhea, usually bloody [63,64]. Children come to medical attention due to symptoms of renal failure. In HUS, thrombocytopenia can be mild in the 50,000 per μL range. Extrarenal involvement is common in typical HUS. Neurologic involvement can be seen in 40% of patients with seizure being the predominant feature. Elevated liver function tests are seen in 40% of patients and 10% of patients will have pancreatitis. Patients with classic HUS will respond to conservative therapy and renal replacement therapy, but severe cases or those with prominent extrarenal manifestations may require response to plasma exchange [65]. Unfortunately, although most patients recover some renal function, many patients will have long-term renal damage.

Atypical HUS

Atypical HUS is best described as HUS without preceding *Escherichia coli* infection [66,67]. This description obviously lacks diagnostic precision, but in general, this term has been applied to HUS which has prominent extrarenal symptomatology, and the prognosis is thought to be worse for atypical HUS [65]. HUS in older patients and HUS without preceding diarrhea may also better be described as having atypical HUS. Therapy for atypical HUS is plasma exchange but the effectiveness of this intervention is debatable [68]. Patients with atypical HUS, especially older patients, may require months of plasma exchange several times each week to control the disease. Chronic renal insufficiency or failure often ensues. Some patients are found to have defects in the regulatory proteins of complement such as factor H [69].

Therapy-Related TTP/HUS

TTP/HUS syndromes can complicate a variety of therapies [70,71]. TTP/HUS can be associated with medications such as cyclosporine, tacrolimus, gemcitabine, and clopidogrel. Cyclosporine/tacrolimus-associated TTP/HUS occurs within days after the agent is started manifesting as a falling platelet count, falling hematocrit, and rising serum LDH level [71,72]. Some cases have been fatal but often the TTP/HUS resolves with decreasing the dose of the calcineurin inhibitor or changing to another agent.

In the past TTP/HUS was most commonly seen with the antineoplastic agent mitomycin C, with a frequency of 10% when a dose of more than 60 mg was used [73]. Anecdotal reports indicated that treatment with staphylococcal A columns was useful for this condition [74]. Now, the most common antineoplastic drug causing TTP/HUS is gemcitabine [75–78]. Like with mitomycin, the appearance of the TTP/HUS syndrome associated with gemcitabine can be delayed, and the condition often is fatal. Severe hypertension often precedes the clinical appearance of the TTP/HUS [79]. The use of plasma exchange is controversial [80], since advanced cancer itself can be associated with a TTP-like syndrome that is typically poorly responsive to plasma exchange. The increasing use of vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and sunitinib has been associated with observation of related TTP/HUS syndromes as well [81–83].

TTP/HUS has been reported with other drugs including the thienopyridines, ticlopidine, and clopidogrel [84]. The frequency of ticlopidine-associated TTP may be as high as 1:1,600, and since this drug was often prescribed for patient with vascular disease, these patients may have been initially misdiagnosed as having recurrent strokes or angina [75,78]. The frequency of TTP using clopidogrel is much less—0.0001%—but since it is widely prescribed, it is the second most common cause of drug-induced TTP [84]. Almost all cases of clopidogrel-induced TTP occur within 2 weeks of starting the drug. All patients with thienopyridine-associated TTP should receive plasma exchange.

TTP/HUS can complicate both autologous and allogeneic hematopoietic stem cell transplants [85–89]. The frequency ranges widely, depending on the criteria used to diagnose TTP/HUS, but it is in the range of 15% for allogeneic and 5% for autologous hematopoietic stem cell transplantation procedures [86,87]. One type, characterized by fulminant multiorgan failure occurs early after transplantation (e.g., within 20 to 60 days), has multiorgan system involvement, is often fatal, and has been associated with severe cytomegalovirus (CMV) infection. Another type of TTP/HUS is similar to cyclosporine/tacrolimus-associated HUS. TTP/HUS that is associated with the conditioning regimen used in the transplantation protocol occurs 6 months or more after total body irradiation, and is associated with primary renal involvement. Finally, patients with systemic CMV infections may present with a TTP/HUS syndrome related to vascular infection with CMV. The etiology of hematopoietic stem cell transplantation-related TTP appears to be different from that of "classic" TTP since alterations of ADAMTS13 have not been found in bone marrow transplant-related TTP implicated in therapy-related vascular damage [90]. The best management of hematopoietic stem cell transplantation-related TTP/HUS is uncertain. Patients should have doses of cyclosporine or tacrolimus decreased, if taking calcineurin inhibitors. Although plasma exchange is often tried, patients with fulminant or conditioning-related TTP/HUS or those with TTP/HUS and concomitant acute graft versus host disease typically do not respond [91–93].

Pregnancy-Related Thrombocytopenic Syndromes

One should consider three syndromes in the critically ill pregnant woman who presents with thrombocytopenia. These are the HELLP syndrome, fatty liver of pregnancy, and TTP (Table 109.7) [94,95].

The acronym HELLP syndrome (**H**emolysis, **E**levated **L**iver tests, **L**ow **P**latelets) describes a variant of pre-eclampsia [96,97]. Classically, HELLP syndrome occurs after 28 weeks of gestation in a patient suffering from pre-eclampsia but can occur as early as 22 weeks in patients with the antiphospholipid antibody syndrome [98]. The pre-eclampsia need not be severe. The first sign of HELLP is a decrease in the platelet count followed by abnormal liver function tests. Signs of hemolysis are present with abundant schistocytes on the smear and a high LDH. HELLP can progress to liver failure and deaths are also reported due to hepatic rupture. Unlike TTP, fetal involvement is present in the HELLP syndrome with fetal thrombocytopenia reported in 30% of cases. In severe cases, elevated D-dimers consistent with DIC are also found. Delivery of the child will most often result in cessation of the HELLP syndrome but refractory cases will require dexamethasone and plasma

TABLE 109.7

PREGNANCY-RELATED DISEASES—TTP/HUS, HELLP SYNDROME, AND ACUTE FATTY LIVER OF PREGNANCY (AFLP)

	HELLP	TTP/HUS	AFLP
Hypertension	Always present	Sometimes present	Sometimes present
Proteinuria	Always present	Sometimes present	Sometimes present
Thrombocytopenia	Always	Always	Always
LDH elevation	Present	Marked	Present
Fibrinogen	Normal to low	Normal	Normal to very low
Schistocytes	Present	Present	Absent
Liver tests	Elevated	Normal	Elevated
Ammonia	Normal	Normal	Elevated
Glucose	Normal	Normal	Low

HELLP, hemolysis, elevated liver tests, and low platelets; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremia syndrome.
Adapted from Sibai [94], Steingrub [95], Egerman and Sibai [104], Esplin and Branch [105].

exchange [99]. About a quarter of women who suffer from HELLP will have a recurrence with a later pregnancy [100].

Fatty liver of pregnancy also occurs late in pregnancy and is only associated with pre-eclampsia in 50% of cases [101–103]. Patients first present with nonspecific symptoms of nausea and vomiting but can progress to fulminant liver failure. Patients develop thrombocytopenia early in the course but in the later stages can develop DIC and very low fibrinogen levels. Mortality rates without therapy can be as high as 90%. Low glucose and high ammonia levels can help distinguish fatty liver from other pregnancy complications [104]. Treatment consists of prompt delivery of the child and aggressive blood product support.

TTP can occur anytime during pregnancy often leading to diagnostic confusion due to the overlap symptoms between TTP and HELLP syndrome [100,104]. There does appear to be a unique presentation of TTP that occurs in the second trimester at 20 to 22 weeks [105]. The fetus is uninvolved with no evidence of infarction or thrombocytopenia if the mother survives. The pregnancy appears to promote the TTP since the TTP will resolve with termination of the pregnancy and can recur with the next pregnancy [106]. Therapy includes terminations of the pregnancy or attempting to support the patient with plasma exchange until delivery. Many patients will have relapses with future pregnancies so this information must be weighed in planning future pregnancies. An unusual complication of pregnancy is a HUS-type syndrome seen up to 28 weeks' postpartum. This form of HUS is severe, and permanent renal failure often results despite aggressive therapy. When evaluated, many of these patients will be found to have defects in regulatory proteins of complement such as factor H deficiency, perhaps explaining the virulence of their renal failure [107].

Disseminated Intravascular Coagulation

At the most basic level, DIC is the clinical manifestation of inappropriate thrombin activation [108–111]. Inappropriate thrombin activation can be due to causes such as sepsis, obstetric disasters, etc. The activation of thrombin leads to (a) conversion of fibrinogen to fibrin, (b) activation of platelets (and their consumption), (c) activation of factors V and VIII, (d) activation of protein C (and degradation of factors Va and VIIIa), (e) activation of endothelial cells, and (f) activation of fibrinolysis.

The clinical manifestations of DIC in a given patient depend on the balance of thrombin activations and secondary fibrinolysis plus the patient's ability to compensate for the DIC. Patients with DIC can present in one of four patterns [108,110]:

1. Asymptomatic. Patients can present with laboratory evidence of DIC but no bleeding or thrombosis. This is often seen in patients with sepsis or cancer. However, with further progression of the underlying disease, these patients can rapidly become symptomatic.
2. Bleeding. The bleeding is due to a combination of factor depletion, platelet dysfunction, thrombocytopenia, and excessive fibrinolysis [108]. These patients may present with diffuse bleeding from multiple sites—IV sites, areas of instrumentation, etc.
3. Thrombosis. Despite the general activation of the coagulation process, thrombosis is unusual in most patients with acute DIC. The exceptions include cancer patients, trauma patients, and certain obstetrical patients. Most often the thrombosis is venous, but arterial thrombosis and nonbacterial thrombotic endocarditis have been reported [112].
4. Purpura fulminans. This severe form of DIC is described in more detail later.

TABLE 109.8

MANAGEMENT OF DISSEMINATED INTRAVASCULAR COAGULATION (DIC): TRANSFUSION

The five basic tests of hemostasis[a]
- Hematocrit
- Platelet count
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Fibrinogen level

Guidelines for transfusion in patients at high risk of bleeding[b]
- A. Platelets < 50,000 per μL: give platelet concentrates or 1 unit of single-donor platelets.
- B. Fibrinogen < 80–100 mg/dL: give 10 units of cryoprecipitate[c]
- C. Hematocrit below 30%: give red cells
- D. Protime > twofold the upper limit of normal *and* aPTT abnormal: give 2–4 units of FFP[d]

[a] These laboratory tests should be repeated after administering blood products serially. A record of the test and the blood products administered should be maintained.
[b] Patients with DIC who are not actively bleeding generally do not require replacement of platelets or coagulation factors, unless an invasive procedure is planned or other circumstances are present; see text.
[c] For a fibrinogen level less then 100 mg/dL, transfusion of 10 units of cryoprecipitate is expected to increase the plasma fibrinogen level by 100 mg/dL.
[d] In patients with DIC and a markedly prolonged PT and aPTT, one can give 2–4 units of fresh frozen plasma (FFP) initially.

The best way to treat DIC is to treat the underlying cause that is driving the thrombin generation [108,109,111, 113,114]. In the past, there was concern about replacement of depleted blood cells and coagulation proteins in DIC due to fears of "feeding the fire." However, such hesitation has not been well validated, and one must provide replacement if depletion occurs and bleeding ensues [115]. Measurement of laboratory tests that will reflect the basic parameters essential for both blood volume and hemostasis may be helpful [18,116]. Replacement therapy is based on the results of these laboratories and the clinical situation of the patient (Table 109.8). Additional discussion regarding transfusion of blood products in critically ill patients is found in Chapter 114. DIC complicating acute promyelocytic leukemia is discussed in detail in Chapter 115.

Heparin therapy is reserved for the patient who has thrombosis as a component of their DIC [109,117,118]. Given the coagulopathy that is often present, one should use specific heparin levels instead of the aPTT to monitor anticoagulation [119,120].

Purpura Fulminans

DIC in association with necrosis of the skin may occur in two situations [121,122]. One, primary purpura fulminans, is most often seen after a viral infection [123]. In these patients, the purpura fulminans starts with a painful red area on an extremity that rapidly progresses to a black ischemic lesion. In many patients, acquired deficiency of protein S is found [121, 124,125].

Secondary purpura fulminans is most often associated with meningococcemia infections, but it can occur in any patient with overwhelming infection [126–128]. Postsplenectomy sepsis syndrome patients and those with functional hyposplenism

due to chronic liver diseases are also at risk [129]. Patients present with signs of sepsis, and the skin lesions often involve the extremities that may lead to amputation. As opposed to primary purpura fulminans, those with secondary purpura fulminans will have symmetrical ischemic at the distal parts of the body (toes and fingers) that ascend as the process progresses. Rarely, adrenal infarction (Waterhouse–Friderichsen syndrome) can occur which leads to severe hypotension [130].

Therapy for purpura fulminans is controversial. Primary purpura fulminans, especially cases with postvaricella autoimmune protein S deficiency, may respond to plasma infusion titrated to keep the protein S level more than 25% [121]. Intravenous immune globulin has also been reported to help decrease the antiprotein S antibodies. Heparin has been reported to control the DIC and extent of necrosis [131]. The starting dose in these patients is 5 to 8 units per kg per hour [109].

Sick patients with secondary purpura fulminans have been treated with plasma drips, plasmapheresis, and continuous plasma ultrafiltration [131–134]. Heparin therapy alone has not been shown to improve survival [135]. Much attention has been given to replacement of natural anticoagulants such as protein C and antithrombin as therapy for purpura fulminans but unfortunately randomized trials using antithrombin have shown mostly negative results [121,125,136–138]. Trials using either zymogen protein C concentrates or rAPC have shown more promise in controlling the coagulopathy of purpura fulminans and improving outcomes in sepsis [132,139–143]. Although bleeding is a concern with use of protein C, most complications occur in patients with platelet counts under 30×10^9/L or in those who have meningitis [144]. If recombinant activated protein C is used, one should also very carefully monitor other parameters of coagulation. Unfortunately, many patients will need debridement and amputation; in one review approximately 66% of patients required amputation [122].

Drug-Induced Hemolytic-DIC Syndromes

A severe variant of the drug-induced immune complex hemolysis associated with DIC has been recognized. Rare patients who receive certain second- and third-generation cephalosporins (especially cefotetan and ceftriaxone) [145] have developed this syndrome [146–151]. The clinical syndrome starts 7 to 10 days after receiving the drug, and often the patient has only received the antibiotic for surgical prophylaxis. Severe Coombs'-positive hemolysis with hypotension and DIC develops. The patients are often believed to have sepsis and often re-exposed to the cephalosporin, resulting in worsening of the clinical status. The outcome is often fatal due to massive hemolysis and thrombosis [148,152–154].

Quinine is associated with a unique syndrome of drug-induced DIC [155–158]. Approximately 24 to 96 hours after quinine exposure, the patient becomes acutely ill with nausea and vomiting. The patient then develops a microangiopathic hemolytic anemia, DIC, and renal failure. Some patients, besides having antiplatelet antibodies, also have antibodies that bind to red cells and neutrophils that may lead to the more severe syndrome. Despite therapy, patients with quinine-induced TTP frequently manifest chronic renal failure.

Treatment of the drug-induced hemolytic-DIC syndrome is based on anecdotal reports. Patients have responded to aggressive therapy including plasma exchange, dialysis, and prednisone. Early recognition of the hemolytic anemia (and the suspicion that it is drug-related) is important for early diagnosis so that the incriminating drug can be discontinued. DIC associated with acute promyelocytic leukemia is discussed in detail in Chapter 115.

Drug-Induced Thrombocytopenia

Patients with drug-induced thrombocytopenia typically present with very low platelet counts 1 to 3 weeks after starting a new medication [159,160]. One of the agents most commonly associated with drug-induced thrombocytopenia in the critical care setting is vancomycin. The thrombocytopenia is acute and severe (below $< 10 \times 10^9$/L), is durably refractory to platelet transfusions, and resolves within days of stopping the drug [161]. In patients with a possible drug-induced thrombocytopenia, the primary therapy is to stop the suspect drug, although patients with severe thrombocytopenia generally should receive platelet transfusions due to the risk of fatal bleeding [159,162]. However, with vancomycin-induced thrombocytopenia, the patient may be refractory to platelet transfusion [161,163]. If there are multiple new medications, the best approach is to stop any drug that is strongly associated with thrombocytopenia [164] (Table 109.9). Immune globulin, corticosteroids, and intravenous anti-D have been suggested as useful in drug-related thrombocytopenia. However, since most of these thrombocytopenic patients recover when the agent is cleared from the body, this therapy is probably not necessary and avoids exposing the patient to additional drug-associated adverse events.

TABLE 109.9

CRITICAL CARE DRUGS COMMONLY IMPLICATED IN THROMBOCYTOPENIA

- Antiarrhythmics
  - Procainamide
  - Quinidine
- Anti-GP IIb/IIIa agents
  - Abciximab
  - Eptifibatide
  - Tirofiban
- Antimicrobial
  - Amphotericin B
  - Fluoroquinolones
  - Rifampin
  - Trimethoprim-sulfamethoxazole
  - Vancomycin
- H_2-blockers
  - Cimetidine
  - Ranitidine
- Acetaminophen
- Bevacizumab
- Carbamazepine
- Danazol
- Efalizumab
- Gold
- Heparin
- Hydrochlorothiazide
- Interferon
- Methyldopa
- Nonsteroidal anti-inflammatory agents
- Trastuzumab
- Quinine

Adapted from DeLoughery [5], George et al. [6], George and Aster [160], Warkentin and Kwon [215], Leal and Robins [216], Cheah et al. [217], Jara et al. [218].

Sepsis

Thrombocytopenia associated with sepsis syndromes classically has been attributed to DIC or destruction by autoimmune mechanisms [165–167]. Increasing evidence, however, points to cytokine-driven hemophagocytosis of platelets [168–171]. Patients with hemophagocytosis appear to have higher rates of multiple organ system failure and higher mortality rates. Inflammatory cytokines, especially monocyte-colony stimulating factor (M-CSF), are thought responsible for inducing the hemophagocytosis [166,172].

Thrombocytopenia may be a diagnostic clue to infection with unusual organisms [173]. Three members of the Ehrlichia family have been reported to cause infections in humans [174,175]. They are transmitted by ticks and the diseases that they produce are similar. Most patients have a febrile illness with high fevers, headaches, and myalgias [174,176]. Patients may have central nervous system signs and marked elevation of the serum levels of liver enzymes. Rarely patients may present with a toxic shock-like syndrome [177]. Although many cases are mild, severe disease is common and the case fatality rate is 2% to 5% [176]. The typical hematologic picture is leukopenia (1.3 to 4 × 10^9 per L) and mild thrombocytopenia (30 to 60 × 10^9 per L). In many patients, the buffy coat reveals the organisms bundled in a 2 to 5 µm morula in the cytoplasm of the granulocytes or monocytes. Consideration of ehrlichiosis is important because highly specific therapy is doxycycline, which is a drug not routinely used for therapy of sepsis syndrome.

The classical hematological presentation of Hantavirus pulmonary syndrome (HPS) can be helpful in the diagnosis of this severe illness. Patients suffer a flu-like prodrome and then rapidly develop a noncardiac pulmonary edema resulting in profound respiratory failure [10,178]. Ventilatory support is required in 75% of cases and the mortality is approximately 50%. A powerful indicator to the presence of Hantavirus is found on the peripheral smear [10,179]. The triad of thrombocytopenia, increased and left-shifted white cell count, and more than 10% circulating immunoblasts can identify all cases of HPS and was seen in only 2.6% non-HPS controls in a recent study [10]. Marked hemoconcentration is also present due to capillary leak syndrome with the hematocrit reaching in some patients as high as 68%.

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers (VHFs) are a diverse group of viral infections that can result in massive bleeding [180–182]. VHFs are an important problem in certain parts of the world but travelers may carry the disease anywhere. In the Southern United States, dengue is becoming an increasing problem and fatal cases of arenavirus have been reported in California [183]. As described in Table 109.10, there are four groups of viruses which can lead to VHFs [184,185].

The typical pattern is a febrile illness that proceeds over a few days to shock and diffuse bleeding with the patient developing signs of thrombocytopenia and in some cases DIC. A key sign is that patients will experience profuse bleeding from the gastrointestinal track and mucosal bleeding often out of proportion to the observed coagulation defects. This finding should serve as a diagnostic clue. Most VHFs are also associated with leukopenia and hemoconcentration. Therapy is aggressive supportive care of the patients and replacement of coagulation factors. As noted in Table 109.10, ribavirin can treat certain VHFs. Given the propensity of many of these infections to spread to healthcare workers, precautions should be taken to prevent nosocomial spread [186].

TABLE 109.10

VIRAL HEMORRHAGIC FEVER-ASSOCIATED THROMBOCYTOPENIA

Arenaviridae
- Diseases: Lassa fever, New World arenaviruses
- Distribution: West Africa (Lassa), South America [rare California] (New World)
- Vector: rodents
- Incubation: 5–16 d
- Therapy: ribavirin
- Unique clinical features: pharyngitis, late deafness (Lassa); neurological involvement–seizures (New World)

Bunyaviridae
- Diseases: Crimean–Congo hemorrhagic virus (CCHF), Rift Valley fever, hemorrhagic fever with renal syndrome (HFRS)
- Distribution: Africa, central Asia, eastern Europe, Middle East (CCHF), Africa, Middle East (Rift), Asia, Balkans, Europe (HFRS)
- Vector: ticks (CCHF), mosquitoes (Rift Valley), rodents (HFRS)
- Incubation: 1–6 d (CHHF), 2 wk to 2 mo (HFRS)
- Therapy: ribavirin
- Unique clinical features: retinitis, hepatitis (Rift Valley), prominent bleeding with DIC, jaundice (CCHF); renal disease (CCHF)

Filoviridae
- Diseases: Ebola, Marburg viruses
- Distribution: Africa
- Vector: ?
- Incubation: 2–21 d
- Unique clinical features: maculopapular rash, high mortality

Flaviviridae
- Diseases: dengue, yellow fever
- Distribution: widespread (dengue), Africa, tropical Americans (yellow)
- Vector: mosquitoes
- Incubation: 3–15 d
- Unique clinical feature: liver involvement (yellow)

Adapted from DeLoughery [185], Nimmannitya [219], Taylor and Strickland [220].

Bleeding in the Platelet-Refractory Patient

Bleeding in patients who are refractory to platelet transfusion presents a difficult clinical problem (Table 109.11) [187,188]. If patients are demonstrated to have HLA antibodies, one can transfuse HLA-matched platelets [189]. Unfortunately, matched platelet transfusions do not work in 20% to 70% of these patients. Also, since some loci are difficult to match, effective products may be unavailable. As many as 25% of patients have antiplatelet antibodies in which HLA-matched products will be ineffective. One can perform platelet crossmatching to find compatible units for these patients but this may not always be successful. In the patient who is totally refractory to platelet transfusion, consider drugs as an etiology of antiplatelet antibodies (especially vancomycin) [163]. Use of antifibrinolytic agents such as epsilon aminocaproic acid or tranexamic acid may decrease the incidence of minor bleeding but are ineffective for major bleeding [190]. “Platelet drips” consisting of infusing either a platelet concentrate per hour or one plateletpheresis unit every 6 hours may be given as a continuous infusion [191,192]. For life-threatening bleeding

TABLE 109.11

EVALUATION AND MANAGEMENT OF PLATELET ALLOIMMUNIZATION

1. Check platelet count 15 min after platelet transfusion.
2. If rise in platelet count is less than 5,000 per μL, check for HLA antibodies.
3. Administer HLA-matched platelets and evaluate for response.
4. If three sequential HLA-matched platelet transfusions are ineffective, discontinue HLA-matched platelets.
5. In completely refractory patients:
   A. Evaluate for other causes of thrombocytopenia (HIT, drugs).
   B. Consider institution of antifibrinolytic therapy
1. Epsilon aminocaproic acid 1 g/h IV, or
2. Tranexamic acid 10 mg/kg IV every 8 h
   C. Platelet "drip"—continuous infusion of platelets at the rate of 1 unit over 6 h
   D. Recombinant activated VII for life-threatening bleeding

rVIIa may be of use [193]. For platelet refractory patients with arterial bleeding, the use of angiographic delivery of platelets has been reported to be successful in stopping bleeding [194].

Catastrophic Antiphospholipid Antibody Syndrome

Rarely patients with antiphospholipid antibody syndrome can present with fulminant multiorgan system failure [195–199]. Catastrophic antiphospholipid antibody syndrome is caused by widespread microthrombi in multiple vascular fields. These patients will develop renal failure, encephalopathy, adult respiratory distress syndrome (often with pulmonary hemorrhage), cardiac failure, dramatic livedo reticularis, and worsening thrombocytopenia. Many of these patients have preexisting autoimmune disorders and high titer-anticardiolipin antibodies. It appears that the best therapy for these patients is aggressive immunosuppression, plasmapheresis, and anticoagulation, then (perhaps) IV cyclophosphamide monthly [198]. Early recognition of this syndrome can lead to quick therapy and resolution of the multiorgan system failure.

Posttransfusion Purpura

Patients with this disorder develop severe thrombocytopenia ($< 10 \times 10^9$ per L), and often severe bleeding, 1 to 2 weeks after receiving blood products [200]. Affected patients usually lack the platelet antigen PLA1. For unknown reasons, exposure to the antigens from the transfusion leads to rapid destruction of the patient's own platelets. The diagnostic clue is thrombocytopenia in a patient, typically female, who has received a red cell or platelet blood product in the past 7 to 10 days. Treatment consists of intravenous immunoglobulin [201] and plasmapheresis to remove the offending antibody. If patients with a history of posttransfusion purpura require further transfusions, only PLA1-negative platelets should be given.

Liver Disease

Patients with severe liver disease have multiple hemostatic defects [202–206] (see Chapter 108, Disorders of Hemostasis). Splenomegaly (due to cirrhosis) and infections (e.g., HCV) may be contributory. Additionally, the liver is the source of thrombopoietin and lack of this platelet growth factor may worsen thrombocytopenia [207–209]. Patients may have platelet dysfunction due to the increase in fibrinogen degradation products and circulating plasmin [210]. Platelet transfusion should be given only to patients with platelet counts that are reliably less than 10×10^9 per L who are actively bleeding, or who require a higher platelet count due to an invasive procedure. The thrombopoietin receptor agonist eltrombopag has been used in patients with HCV-associated thrombocytopenia enabling administration of eradication therapy for HCV [211], but the delayed onset of action may make use in the critical care unit, where a need for immediate correction in the platelet count is more likely to be encountered, less feasible.

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CHAPTER 110 ■ ANTITHROMBOTIC PHARMACOTHERAPY

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INTRODUCTION

Thromboembolic disease is commonly encountered among critically ill patients [1]. While these patients are at high risk for developing arterial and venous thrombosis due to underlying comorbidities, central venous catheter placement, and immobility, they are also at high risk for hemorrhagic complications resulting from gastrointestinal stress ulcerations, invasive procedures, liver dysfunction, uremia, or coagulopathy [2]. These divergent features often complicate antithrombotic treatments for prevention or management of thrombosis. Limitations in administration routes, hemodynamic instability, alterations in renal and hepatic function, and drug interactions further complicate the administration of these high-risk medications [3].

This chapter focuses on the mechanism of action, pharmacokinetics, pharmacodynamics, clinical indications, complications of therapy, and reversal options for antithrombotic pharmacotherapy in critically ill patients.

ANTIPLATELET PHARMACOTHERAPY

Overview of Antiplatelet Pharmacotherapy

Antiplatelet agents target mechanisms in platelet activation, adhesion, and aggregation. Pharmacological inhibitors of platelet function fall into four general categories: thromboxane (TXA) inhibitors, antagonists of adenosine diphosphate (ADP)-mediated platelet activation, glycoprotein (GP) IIb/IIIa inhibitors, and phosphodiesterase inhibitors (Fig. 110.1).

Antiplatelet "resistance" and "nonresponse" are terms applied to clinical outcomes characterized by failure to prevent a thrombotic event due to inadequate platelet inhibition [4]. Resistance is conferred by underlying clinical, cellular, and genetic mechanisms. It is best confirmed by platelet function testing [5]. While several methods are available for measuring overall and drug-specific platelet aggregation, standard testing protocols have yet to be established [6].

Aspirin and Aspirin Derivatives

Pharmacology, Pharmacodynamics, and Monitoring

Aspirin, or acetylsalicylic acid, is a prodrug of salicylic acid that blocks platelet activation. Aspirin irreversibly inhibits both cyclooxygenase enzymes (COX-1, COX-2), reducing prostaglandin and TXA byproducts generated from arachidonic acid. Thromboxane A_2 stimulates platelet activation, aggregation, and recruitment. COX-1 enzymes are present in most tissues, but larger amounts are found in the stomach, kidneys, and platelets. The prostaglandin products of COX enzyme activity provide protection from gastrointestinal mucosal injury. COX-2 is found in both nucleated and nonnucleated cells and is responsive to inflammatory stimuli. Inhibition of COX-1 appears to be the primary mechanism by which aspirin inhibits hemostasis. The acetylation of platelet COX-1 enzymes by aspirin causes inhibition of platelet TXA_2 production. The irreversible antiplatelet effect lasts for the life of platelet (7 to 10 days). Saturation of the mechanism occurs at doses as low as 30 mg. Large doses of aspirin (> 3,000 mg daily) are required to inhibit COX-2 and produce systemic anti-inflammatory effects. Consequently, there is a 50- to 100-fold variation between the daily doses required to suppress inflammation and inhibit platelet function [7,8].

Enteric-coated and delayed release formulations have diminished bioavailability, take 3 to 4 hours to reach peak plasma levels, and have delayed onset. Rectally administered aspirin has variable absorption with a bioavailability of 20% to 60% over a 2- to 5-hour retention time [9]. For acute thrombosis, immediate-release aspirin is preferred [10].

The optimal aspirin dose that maximizes efficacy and minimizes toxicity is controversial. Evidence-based recommendations vary from 75 to 325 mg daily. There is currently no data suggesting inferiority of lower (75 to 100 mg) to higher (> 100 mg) maintenance dosing in preventing thromboembolic events [11].

Recurrent vascular thrombotic episodes despite aspirin therapy occur at rates between 2% and 6% of patients per year [4]. Aspirin resistance occurs in 5.5% to 45% of aspirin-treated patients. Possible mechanisms of aspirin resistance

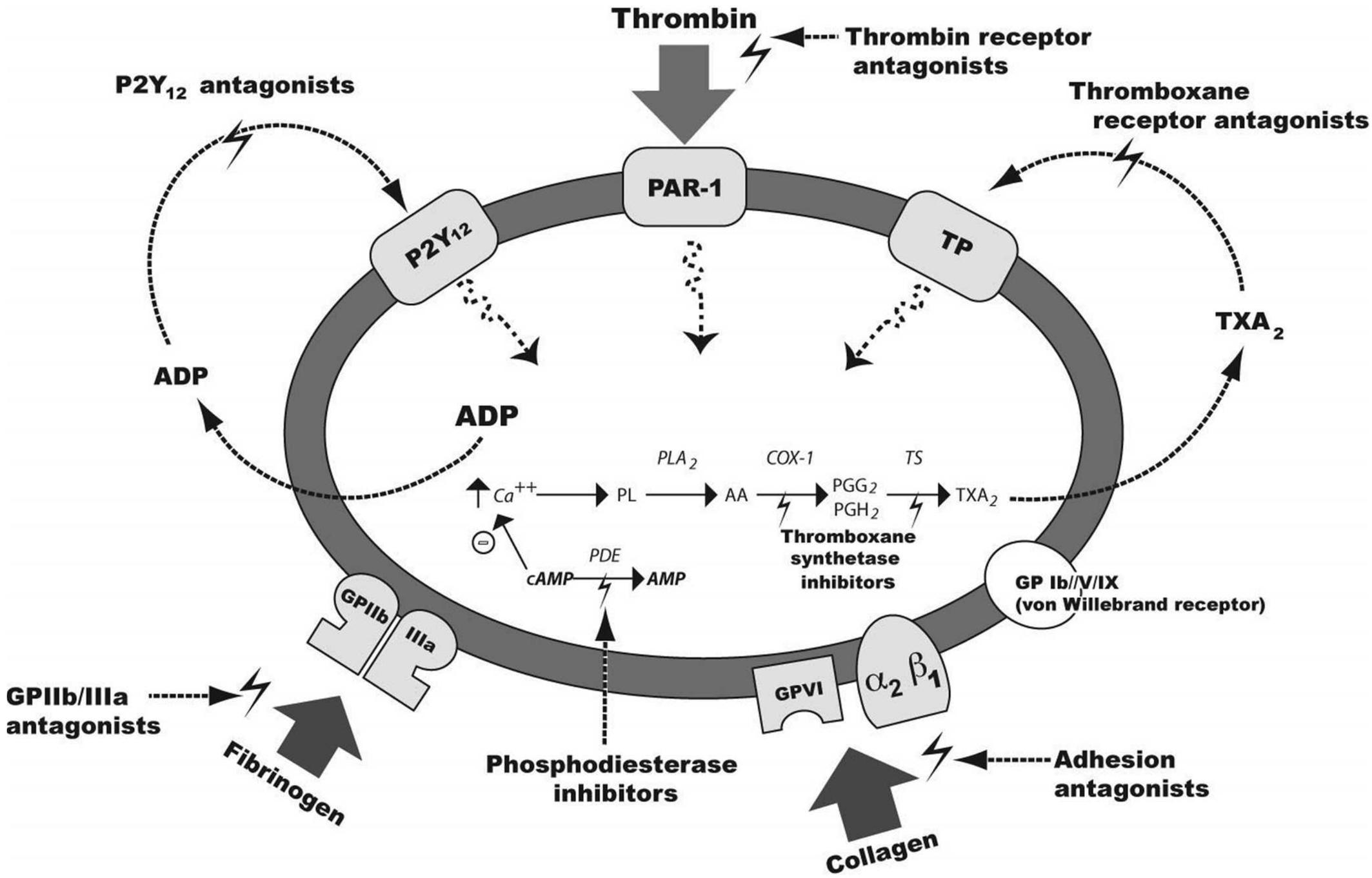

FIGURE 110.1. Platelet activation and pharmacological inhibitors of platelet function. Platelet activation involves four mechanisms: adhesion to sites of vascular injury, release of stimulatory compounds, aggregation, and priming of coagulation. Pharmacological inhibitors of platelet function target adhesion, release, and aggregation mechanisms. Platelet adhesion is a four-step process involving tethering of von Willebrand factor (VWF) to glycoprotein (GP) Ib platelet receptors, a potential target of investigational agents. The rolling phase of adhesion involves interaction between vascular collagen with GP VI and GP Ia/IIa receptors, another potential target of investigational agents. The activation phase of adhesion involves release of thromboxane A_2 (TXA_2) and adenosine diphosphate (ADP) which can be blocked with use of aspirin and $P2Y_{12}$ inhibitors, respectively. The stable adhesion phase involves the interaction of GP IIb/IIIa receptors with fibrinogen and VWF, which can be blocked with the use of GP IIb/IIIa inhibitors.

include extrinsic factors (compliance, absorption, dosage formulation, and smoking) and intrinsic factors (pharmacodynamic alterations, receptor polymorphisms, upregulation of nontargeted platelet activation pathways). In clinical trials, aspirin resistance has been associated with an increased risk of death, acute coronary syndromes (ACS), and stroke [5,12,13].

Clinical Indications

Aspirin is indicated for the primary and secondary prevention of arterial and venous thrombosis (Table 110.1). Aspirin is effective in reducing atherothrombotic disease morbidity and mortality in ACS, stable angina, coronary bypass surgery, peripheral arterial disease (PAD), transient ischemic attack, acute ischemic stroke, and polycythemia vera. A meta-analysis of 145 randomized studies in patients with coronary artery and cerebrovascular disease demonstrated that aspirin 75 to 300 mg per day reduced the risk of nonfatal myocardial infarction (MI) by 35% and the risk of vascular events by 18% [14]. Aspirin provides effective thromboprophylaxis in patients on warfarin with prosthetic heart valves and in patients with nonvalvular atrial fibrillation [15].

Complications and Reversal of Effect

Aspirin increases the incidence of major, gastrointestinal, and intracranial bleeding [15]. The recommended interval for discontinuation of aspirin prior to elective surgery or procedures is 7 to 10 days. Therapy can be resumed approximately 24 hours or the next morning after surgery when there is adequate hemostasis [16]. For patients exhibiting clinically significant bleeding or requiring emergent surgery, platelet transfusion may be warranted. Intravenous desmopressin antagonizes aspirin's effect, suggesting a role in emergent situations as well [17].

Aspirin produces gastrointestinal ulcerations and hemorrhage through direct irritation of the gastric mucosa and via inhibition of prostaglandin synthesis. Aspirin, in recommended doses, increases the risk of gastrointestinal bleeding 1.5- to 3-fold [14,18]. Enteric-coated and buffered aspirin doses $\leq$325 mg do not reduce the incidence of gastrointestinal bleeding [19]. Aspirin-induced gastric toxicity can be prevented with concurrent use of acid-suppressive therapy [20].

Underlying aspirin allergy can exacerbate respiratory tract disease, angioedema, urticaria, or anaphylaxis and is estimated

TABLE 110.1

CLINICAL USES OF ASPIRIN

Drug	Indications	Dosing, timing, duration	Precautions
Acetylsalicylic acid (aspirin)	Treatment of acute coronary syndromes	Load 162–325 mg orally Initial dosing for stents 162–325 mg orally/d: Bare metal 1 mo Sirolimus 3 mo Paclitaxel 6 mo Maintenance: 81–325 mg/d orally	■ Thrombocytopenia ■ Bleeding disorders ■ Pregnancy (third trimester) ■ Gastrointestinal disorders ■ Renal failure ■ Severe hepatic insufficiency ■ Concomitant antithrombotic medication use ■ Alcohol consumption
	Primary and secondary prevention of myocardial infarction in patients with chronic stable angina, previous MI, or unstable angina	81–325 mg/d orally	
	Secondary prevention in stroke and TIA patients	75–325 mg/d orally	
	Acute thrombotic stroke	160–325 mg/d, initiated within 48 h (in patients who are not candidates for fibrinolytics and are not receiving systemic anticoagulation)	
	Secondary prevention in CABG, carotid endarterectomy patients	75–325 mg/d starting 6 h following procedure; if bleeding prevents administration at 6 h after CABG, initiate as soon as possible	

CABG, coronary artery bypass graft; MI, myocardial infarction; TIA, transient ischemic attack.

to occur in 10% of the general population. These patients may be converted to alternative antiplatelet therapies. Leukotriene-modifying agents may reduce aspirin-provoked respiratory reactions but do not eliminate the risk. For patients with a compelling indication for therapy, aspirin desensitization may be considered [21].

$P2Y_{12}$ Inhibitors

Pharmacology, Pharmacodynamics, and Monitoring

$P2Y_{12}$ inhibitors prevent platelet activation by blocking ADP binding to $P2Y_{12}$ receptors. This action prevents activation of the GP IIb/IIIa receptor complex on the platelet surface [10].

Thienopyridine derivatives, clopidogrel, prasugrel, and ticlopidine, are prodrugs requiring hepatic activation via the cytochrome P450 (CYP450) isoenzyme system (Table 110.2). Metabolism by CYP450 plays a key role in the onset of action, potency, and drug interaction profile of these agents [22,23]. A loading dose provides a rapid increase in plasma concentration and a faster onset of action. Both clopidogrel and ticlopidine require a two-step activation process via CYP450. Prasugrel undergoes one-step oxidation by multiple CYP450 isoenzyme pathways which are believed to be responsible for its more predictable action.

While thienopyridine metabolites have a short plasma elimination half-life (1 to 8 hours), their irreversible activity at $P2Y_{12}$ receptors spans the life of the platelet (7 to 10 days). The onset of action, duration of antiplatelet effect, and unpredictable levels of platelet inhibition have led to the development of newer agents [24–26]. Three investigational nonthienopyridine derivatives are currently under investigation for the management of ACS. These agents do not require hepatic activation resulting in immediate, short-acting, dose-dependent inhibition of platelet aggregation [26].

Resistance to clopidogrel occurs in 4% to 34% of patients and depends on the agent, type, and timing of platelet function test, as well as underlying comorbidities such as diabetes and obesity [23]. Possible mechanisms of $P2Y_{12}$ inhibitor resistance include extrinsic factors and intrinsic factors. Recent literature highlighted the importance of genetic and drug-induced alterations of CYP3A4 enzymes, the pathway responsible for thienopyridine activation [27]. Clopidogrel resistance has been associated with an increased risk of death, MI, and stroke. For patients with presumed or confirmed clopidogrel resistance, maintenance dosing up to 150 mg daily or use of more potent agents may be necessary, particularly in patients with in-stent thrombosis [27].

Monitoring the antiplatelet effect of $P2Y_{12}$ inhibitors using platelet function testing is an evolving area of research [27]. The high incidence of varied responses to thienopyridines due to CYP450 polymorphisms and potential drug interactions have suggested a strategy for improving response by using point-of-care platelet function testing.

Clinical Indications

$P2Y_{12}$ inhibitors are indicated for primary and secondary thrombosis prevention in a variety of disease states (Table 110.3). Ticlopidine reduces thrombotic events in patients with stroke, but is associated with neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura [28]. Clopidogrel is indicated alone or in combination with aspirin for primary and secondary prevention of ischemic events in ACS, PAD, stroke, and coronary artery disease. Prasugrel is indicated alone or in combination with aspirin for the prevention of thrombotic cardiovascular events, including in-stent

TABLE 110.2

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF $P2Y_{12}$ INHIBITORS

	Ticlopidine	Clopidogrel	Prasugrel	Ticagrelor[a]	Cangrelor[a]	Elinogrel[a]
Route	Oral	Oral	Oral	Oral	IV	Oral/IV
Receptor binding	Irreversible	Irreversible	Irreversible	Reversible	Reversible	Reversible
Prodrug	Yes	Yes	Yes	No	No	No
Metabolism	CYP3A4	CYP3A4, 2B6	CYP3A4, 2B6, 2C9, 2C19	CYP3A4	Plasma esterase	Not reported
Clearance	Renal 60% Fecal 23%	Renal 50% Fecal 46%	Renal 68% Fecal 27%	Renal 1%	—	Renal 52% Fecal 48%
Time to peak platelet inhibition	2–5 d	300 mg LD: 6 h 600 mg LD: 2 h	1–2 h	2 h	30 min	20 min (IV)
Duration of antiplatelet effect	7–10 d	7–10 d	7–10 d	1 d	20–60 min	1 d
Genetic polymorphisms	Yes	Yes	No	No	Not reported	Not reported

[a]Investigational agent.
IV, intravenous; CYP, cytochrome P; LD, loading dose.

thrombosis, in ACS patients who are managed with percutaneous coronary intervention (PCI) [23].

Complications and Reversal of Effect

The incidence of major bleeding with $P2Y_{12}$ inhibitors varies between agents, dosing, patient populations, and concomitant antithrombotic therapies. Gastrointestinal hemorrhage is a common complication of $P2Y_{12}$ inhibitor therapy [20]. Endoscopic evaluations at 1 week demonstrated less gastrointestinal damage with clopidogrel 75 mg daily than with aspirin 325 mg daily [29]. For patients exhibiting clinically significant bleeding, platelet transfusion may be warranted.

$P2Y_{12}$ inhibitors should be avoided in patients undergoing neuraxial analgesia due to the risk of subdural hematoma [30]. Therapy should be discontinued 7 to 10 days prior to elective surgery or invasive procedure and resumed approximately 24 hours or the next morning after surgery.

TABLE 110.3

CLINICAL USES OF $P2Y_{12}$ INHIBITORS

Drug	Indications	Dosing, timing, duration	Precautions
Clopidogrel (Plavix™)	Treatment of acute coronary syndromes +/− percutaneous intervention	Load 300 mg × 1 PCI load: 300–600 mg × 1 Maintenance 75 mg/d orally Drug-eluting stents: duration of clopidogrel ideally 12 mo following drug-eluting stent	■ Age > 75 y (prasugrel) ■ Interruption of clopidogrel may cause in-stent thrombosis with subsequent fatal and nonfatal myocardial infarction
	Primary and Secondary prevention of myocardial infarction in patients with chronic stable angina, previous MI, or unstable angina Cerebrovascular accident Arteriosclerotic vascular disease Peripheral arterial occlusive disease	75 mg orally once daily	■ Indwelling epidural catheter ■ Combination of aspirin and clopidogrel in patients with recent TIA or stroke ■ Liver disease ■ Thrombotic thrombocytopenic purpura may occur (rare) ■ Recent trauma, surgery/biopsy ■ Hematologic disorders
Ticlopidine (Ticlid™)	Placement of stent in coronary artery Secondary prevention in thromboembolic stroke	250 mg orally twice a day	■ Discontinue if ANC less than 1,200/μL or platelet count less than 80,000/μL (ticlopidine) ■ Elevated triglycerides (ticlopidine)
Prasugrel (Effient™)	Treatment of acute coronary syndromes +/− percutaneous intervention	Load 60 mg × 1 Maintenance: 10 mg/d orally Weight < 60 kg, consider using a lower maintenance dose of 5 mg/d	

ANC, absolute neutrophil count; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

TABLE 110.4

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF GLYCOPROTEIN IIB/IIIA INHIBITORS

	Abciximab	Eptifibatide	Tirofiban
Agent type	Fab fragment of human–mouse chimeric monoclonal antibody	Cyclic heptapeptide	Nonpeptide
Antigenicity	Yes	No	No
Receptor binding effect	Reversible	Reversible	Reversible
Receptor affinity	High	Moderate	Moderate
Excretion	Renal and reticuloendothelial system	50% renal	39%–69% renal
Dosage reduction in renal failure	No	Yes, decrease infusion dose by 50% if CrCl < 50 mL/min	Yes, decrease infusion dose by 50% if CrCl < 30 mL/min
Removable by dialysis	No	Yes	Yes
Duration of antiplatelet effect	24–48 h	4–8 h	4–8 h

CrCl; creatinine clearance using Cockcroft–Gault equation.

Glycoprotein IIb/IIIa Inhibitors

Pharmacology, Pharmacodynamics, and Monitoring

GP IIb/IIIa receptors are expressed on the platelet surface, with approximately 50,000 to 80,000 copies per platelet. Blocking GP IIb/IIIa receptors prevents platelet activation, aggregation, and fibrinogen-mediated platelet to platelet bridging.

Intravenous GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) vary in their structure and pharmacokinetic properties (Table 110.4) [10,31]. Although the exact threshold required for efficacy with these agents has not been established, > 80% platelet inhibition is thought to be a target associated with adequate antiplatelet activity in patients with ACS and in those undergoing PCI [32].

Abciximab is a human–murine chimeric monoclonal antibody that demonstrates a dose-dependent inhibition of GP IIb/IIIa receptors. After an initial intravenous bolus and infusion, the onset of platelet inhibition is rapid (5 minutes) and 80% to 90% of ADP-induced platelet aggregation is suppressed [31]. Abciximab has a strong affinity for the receptor, resulting in occupancy that persists for weeks. Once discontinued, platelet function recovers gradually, with bleeding time normalizing at 12 hours and ADP-induced aggregation returning at 24 to 48 hours [31,32].

Both eptifibatide, a synthetic peptide, and tirofiban, a synthetic small molecule, demonstrate high selectivity, but reduced affinity for the GP IIb/IIIa receptor when compared to abciximab. Both exhibit platelet inhibition that is linear and dose dependent. An intravenous eptifibatide or tirofiban bolus dose followed by an infusion provides > 80% inhibition of ADP-induced platelet aggregation. For patients undergoing PCI, a second eptifibatide bolus 10 minutes after the initial dose further enhances platelet inhibition at 1 hour. Since both agents dissociate from the GP IIb/IIIa receptor rapidly, normal platelet aggregation is restored within 4 to 8 hours after drug discontinuation [33–35].

Platelet counts should be monitored within the first 24 hours while taking GP IIb/IIIa inhibitors. For abciximab, platelet counts should be evaluated within 2 to 4 hours of initiation due to a higher risk of thrombocytopenia.

Clinical Indication

GP IIb/IIIa inhibitors are included in evidence-based guidelines as adjunctive therapy for patients with ACS and those undergoing PCI (Table 110.5).

Optimal use of GP IIb/IIIa inhibitors involves appropriate patient risk stratification, use with other antithrombotic agents, appropriate dose, and duration of therapy [36].

Complications and Reversal of Effect

The frequency of major bleeding with GP IIb/IIIa therapy ranges from 1% to 14% of patients and depends on the agent, concomitant therapies, and settings of ACS or PCI [32–34]. Failure to adjust dosing in renal dysfunction further increases the risk of bleeding [37]. Factors associated with bleeding risk include age, female gender, body weight, diabetes, congestive heart failure, renal function, concomitant fibrinolytic use, prolonged femoral sheath placement, and heparin dosing [38,39].

The duration of the antiplatelet effect is agent specific and is influenced by platelet binding (abciximab binds to platelets for up to 10 days) and renal function (tirofiban and eptifibatide have half-lives of 1.5 to 3 hours with normal renal function). An intravenous desmopressin dose of 0.3 μg per kg may be beneficial in reducing bleeding time [17].

Nonhemorrhagic side effects of GP IIb/IIIa inhibitors include severe thrombocytopenia. The incidence of thrombocytopenia with eptifibatide and tirofiban is similar to placebo, with rates ranging from 0.2% to 0.3% of treated patients. With abciximab, the incidence is reported as 5%; however, up to 4% of cases can be due to pseudothrombocytopenia as a result of platelet clumping. The onset of thrombocytopenia usually occurs within the first 24 hours of infusion, but delayed onset has been reported [40,41].

Platelet or red blood cell transfusions may be warranted for patients with persistent thrombocytopenia or clinically significant bleeding and must take into account drug concentrations in the plasma or drug bound to platelets [31]. Abciximab has been associated with antibody formation in 6% of patients. The risk of thrombocytopenia and immune-mediated reactions may limit repeat use [8,10,32]. GP IIb/IIIa inhibitor administration should be avoided in patients requiring neuraxial analgesia due to risk of subdural hematoma [30].

Dipyridamole

Pharmacology, Pharmacodynamics, and Monitoring

Dipyridamole inhibits adenosine binding to platelets and endothelial cells. The increase in adenosine leads to a rise in cyclic adenosine monophosphate (cAMP), which in turn decreases platelet responsiveness to various stimuli. Dipyridamole is

TABLE 110.5

CLINICAL USES OF GLYCOPROTEIN IIB/IIIA INHIBITORS

Drug	Indications	Dosing, timing, duration	Precautions
Eptifibatide (Integrilin™)	Treatment of acute coronary syndromes +/− percutaneous coronary intervention	IV bolus 180 µg/kg ABW (maximum 22.6 mg) as soon as possible, followed by 2 µg/kg ABW/min (maximum 15 mg/h) infusion until discharge or CABG surgery, up to 72 h If undergoing PCI, administer a second 180 µg/kg IV bolus 10 min after the first and continue the infusion up to discharge, or for up to 18–24 h after procedure, whichever comes first, allowing for up to 96 h of therapy Renal adjustment CrCl < 50 mL/min, 180 µg/kg actual body weight (maximum 22.6 mg) IV bolus as soon as possible, followed by 1 µg/kg/min (maximum 7.5 mg/h) infusion	■ Concomitant use of fibrinolytics, anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory agents ■ Indwelling epidural catheter ■ Do not remove arterial sheath unless aPTT is less than 45 s or ACT less than 150 s and heparin discontinued for 3–4 h ■ Platelet count below 150,000/µL ■ Renal insufficiency (eptifibatide) ■ Severe renal insufficiency, chronic hemodialysis (tirofiban) ■ Readministration of abciximab may result in hypersensitivity, thrombocytopenia, or diminished benefit due to antibody formation ■ Hemorrhagic retinopathy
Abciximab (Reopro™)	Treatment of acute coronary syndromes +/− percutaneous coronary intervention	Initial, 0.25 mg/kg IV bolus (over 5 min), followed by 0.125 µg/kg/min (maximum 10 µg/min) IV infusion for 12 h in combination with fibrinolytic treatment or after PCI, unless complications No adjustment required for renal dysfunction	
Tirofiban (Aggrastat™)	Treatment of acute coronary syndromes	0.4 µg/kg/min IV for 30 min, then 0.1 µg/kg/min for 12–24 h after PCI Severe renal impairment (CrCl less than 30 mL/min): give half the usual dose–0.2 µg/kg/min IV for 30 min, then 0.05 µg/kg/min	

ABW, actual body weight; ACT, activated clotting time; aPTT, activated thromboplastin time; CABG, coronary artery bypass graft; CrCl; creatinine clearance using Cockcroft–Gault equation; IV, intravenous; PCI, percutaneous coronary intervention.

metabolized hepatically and has a half-life of approximately 10 hours [10].

Clinical Indications

Dipyridamole is indicated as adjunctive therapy for the prevention of thromboembolism in patients with cardiac valve replacement. Combined with aspirin, dipyridamole is indicated for secondary prevention of cerebrovascular accidents and TIA. The combination of aspirin and extended-release dipyridamole was associated with reductions in major vascular events in patients with stroke or TIA (Table 110.6) [10,42].

Complications and Reversal of Effect

While headache is the most common adverse effect associated with dipyridamole therapy, hemorrhage may also occur. For patients exhibiting clinically significant bleeding, platelet transfusion may be warranted.

Cilostazol

Pharmacology, Pharmacodynamics, and Monitoring

Cilostazol blocks platelet activation via phosphodiesterase 3 (PDE3) inhibition. PDE3 inhibition increases cAMP concentrations resulting in inhibition of platelet aggregation and an increase in vasodilation [43].

Cilostazol is extensively metabolized by CYP 450-3A4 subclass. Avoidance of therapy or reduced dosing may be required for patients taking potent CYP3A4 inhibitors [44].

Clinical Indication

Cilostazol is indicated for treatment of intermittent claudication symptoms and has shown benefit in reducing symptoms and improving walking distance [44].

Complications and Reversal of Effect

Nonhemorrhagic complications of cilostazol therapy include headache, peripheral edema, and tachycardia [44].

Overview of Anticoagulant Pharmacotherapy

Blood coagulation has been summarized previously in Chapter 108. Anticoagulant agents inhibit thrombosis and propagation by inhibiting thrombin directly or indirectly by attenuating thrombin generation (Fig. 110.2). Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are effective in acute thrombosis due to their rapid onset. Since heparins are dependent on the presence of antithrombin (AT) for clotting factor inhibition, they are considered indirect anticoagulants. Heparins contain a pentasaccharide sequence that binds to AT, producing a conformational change that accelerates AT inactivation of coagulation factors XIIa, IXa, XIa, Xa, and IIa (thrombin). Of these, thrombin and Xa play the most critical role in the coagulation cascade. The active pentasaccharide sequence responsible for catalyzing AT is found on one-third and one-fifth of the chains of heparin and LMWH, respectively. Fondaparinux is a synthetic analog of this naturally occurring pentasaccharide [45–47].

TABLE 110.6

CLINICAL USES OF PHOSPHODIESTERASE INHIBITORS

Drug	Indications	Dosing, timing, duration	Precautions
Dipyridamole (Persantine™)	Radionuclide myocardial perfusion study VTE prophylaxis after heart valve replacement	0.142 mg/kg/min IV for 4 min (0.57 mg/kg total) prior to thallium; maximum 60 mg With concomitant warfarin therapy: 75–100 mg orally four times daily	■ Aminophylline injection should be readily available for relieving adverse effects such as chest pain and bronchospasm ■ Hypotension ■ Severe coronary artery disease, abnormal cardiac rhythm ■ Avoid in patients with severe hepatic insufficiency ■ Avoid in patients with severe renal failure (CrCl less than 10 mL/min) ■ Severe coronary artery disease ■ Coagulation abnormalities ■ Severe renal impairment
Dipyridamole extended-release/aspirin (Aggrenox™)	Secondary prevention in stroke and TIA patients	200 mg dipyridamole, 25 mg aspirin (1 capsule) orally twice daily Patients with intolerable headache 200 mg dipyridamole, 25 mg aspirin orally daily at bedtime, with 81 mg of aspirin in the morning Return to usual dose as soon as tolerance to headache develops (usually within a week)	
Cilostazol (Pletal™)	Intermittent claudication	100 mg orally twice a day	

CrCl, creatinine clearance using Cockcroft–Gault equation; IV, intravenous; TIA, transient ischemic attack; VTE, venous thromboembolism.

Unfractionated Heparin

Pharmacology, Pharmacodynamics, and Monitoring

UFH is composed of a heterogeneous mixture of highly sulfated polysaccharide chains that vary in molecular weight, anticoagulant activity, and pharmacokinetic properties. A minimum of 18 saccharide units are required for UFH to form a ternary complex with AT and inhibit thrombin. Once bound to AT molecules, UFH can readily dissociate and bind to other AT molecules. Alternatively, the only requirement for factor Xa inhibition is for the heparin-AT complex to be formed. Heparin has equal inhibitory activity against factor Xa and thrombin, binding in a 1:1 ratio.

Since UFH is poorly absorbed orally, intravenous or subcutaneous injections are the preferred administration routes [47]. When given as subcutaneous injection with therapeutic intent, UFH doses need to be large enough (> 30,000 units per day) to overcome erratic bioavailability. UFH readily binds to plasma proteins after parenteral administration which contributes to variable anticoagulant response. Despite these limitations, intravenous administration rapidly achieves therapeutic plasma concentrations that can be monitored and adjusted based on infusion rates [45].

UFH clearance from systemic circulation is dose related and occurs through two independent mechanisms [46,48]. The initial phase is rapid and saturable binding to endothelial cells, macrophages, and local proteins where UFH is depolymerized. The second phase is a slower, nonsaturable, renal-mediated clearance. At therapeutic doses, UFH is cleared primarily in the initial phase with higher-molecular-weight chains being cleared more rapidly than lower-weight counterparts. As elimination becomes dependent on renal clearance, increased or prolonged UFH dosing provides a disproportionate increase in both the intensity and duration of anticoagulant effect. With therapeutic intravenous doses of heparin, the half-life of UFH is approximately 60 minutes [46,48].

The anticoagulant response to UFH is monitored using activated partial thromboplastin time (aPTT), a measurement sensitive to the inhibitory effects of thrombin. The aPTT should be measured every 6 hours, and doses adjusted accordingly, until the patient sustains therapeutic levels. Once steady state is reached, the frequency of monitoring can be extended.

Weight-based dosing nomograms are recommended for treatment of thromboembolic disease. Such nomograms have been associated with a shorter time to reach a therapeutic level without an increase in bleeding events. Heparin dosing nomograms differ between hospitals due to differences in thromboplastin agents and interlaboratory standards in aPTT measurements [49].

Clinical Indications

Clinical indications for UFH include treatment of ACS, treatment or prevention of venous thromboembolism (VTE), bridge therapy for atrial fibrillation, and cardioversion (Table 110.7) [36,48,50]. Due to UFH's short half-life and reversibility, it remains the best option in patients with bleeding risk or organ dysfunction. Patients with fluctuating renal function or a calculated creatinine clearance less than 30 mL per minute are not candidates for LMWH or fondaparinux due to the risk of accumulation and increased bleeding risk, and should be given UFH [51]. When used for thromboprophylaxis in medical patients, three times daily heparin dosing provides better efficacy in reducing VTE events compared to twice daily dosing, but generates more major, but not minor, bleeding episodes [52].

Complications and Reversal of Effect

The major complications of UFH therapy include bleeding (major bleeding, 0% to 7%; fatal bleeding, 0% to 3%), heparin-induced thrombocytopenia (1% to 5%), and osteoporosis (2% to 3% risk of vertebral fracture with less than 1 month of treatment) [53]. Hemorrhagic episodes are associated with anticoagulation intensity, route of administration (continuous infusions are associated with lower rates), and concomitant use of

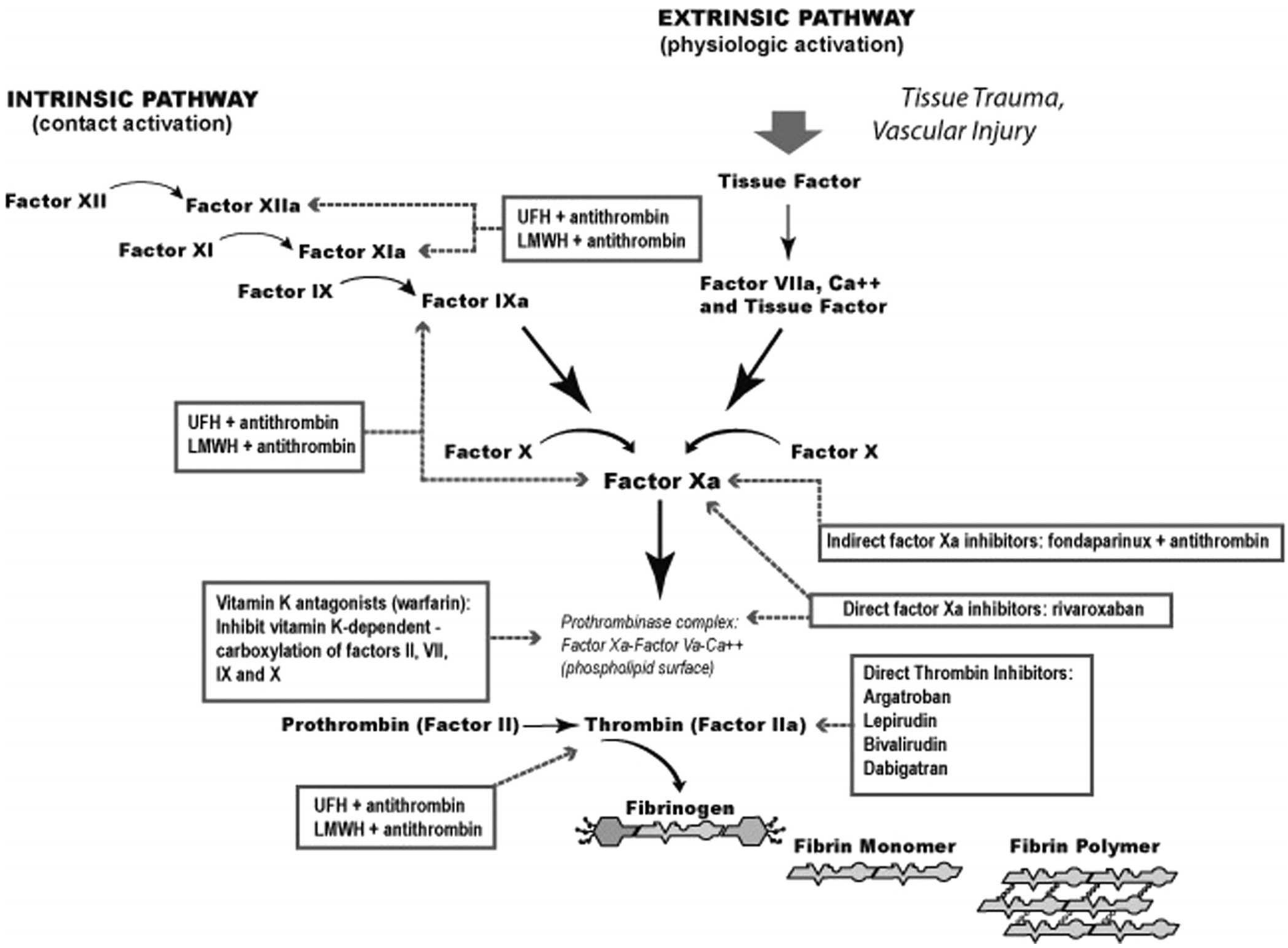

FIGURE 110.2. The coagulation cascade comprises the intrinsic (contact activation) pathway and the extrinsic (tissue factor) pathway. Each pathway generates a series of reactions in which inactive circulating enzymes and their cofactors are activated. These activated factors then catalyze the next reaction in the cascade. Thrombin plays a pivotal role by triggering the conversion of soluble fibrinogen in insoluble fibrin monomers, which serve as the foundation for thrombus formation. Thrombin also activates factors VIII, V, and XIII. Factor XIII generates the covalent bonds that link fibrin strands, ensuring structural integrity. Anticoagulants, either through their interaction with antithrombin, or through a direct inhibition of thrombin, interrupt these enzymatic reactions.

TABLE 110.7

CLINICAL USES OF UNFRACTIONATED HEPARIN

Drug	Indications	Dosing, timing, duration	Precautions
Unfractionated heparin	Treatment of VTE	80 units/kg bolus, then 18 units/kg/h infusion adjusted per local heparin nomogram	■ Allergic or hypersensitivity-type reactions ■ Congenital or acquired bleeding disorders ■ Indwelling epidural catheter ■ Gastrointestinal ulceration and ongoing tube drainage of the small intestine or stomach ■ Hepatic disease with impaired hemostasis ■ Hereditary antithrombin III deficiency and concurrent use of antithrombin ■ Menstruation ■ Neonates and infants weighing < 10 kg ■ Premature infants weighing less than 1 kg
	Treatment of ACS	IV bolus: 60 units/kg (max 4,000 units) 12 units/kg/h (max 1,000 units) +/− fibrinolysis, adjusted to maintain aPTT 1.5–2 times control or per local heparin nomogram	
	Bridge therapy for atrial fibrillation, cardioversion	IV infusion: 60–80 units/kg bolus Target aPTT, 60 s, range, 50–70 s	
	Prophylaxis of VTE in the medically ill or surgical population	5,000 units SC every 8–12 h	
	Prophylaxis of VTE in pregnancy (with prior VTE)	7,500–15,000 units SC every 12 h	

ACS, acute coronary syndrome; aPTT, activated partial thromboplastin time; IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.

TABLE 110.8

PROTAMINE DOSE CALCULATION FOR UNFRACTIONATED HEPARIN REVERSAL

UFH delivery time (h)	Heparin dose	Patient weight (kg)	Intravenous UFH dose administered (units)	UFH accumulation at 1 h[a,b] (units)	UFH remaining at 2 h[a,b] (units)	UFH remaining at 3 h[a,b] (units)	Protamine dose (mg) required to reverse UFH[c]
0	80 units/kg bolus	80	6,400	3,200	1,600	800	8
0	18 units/kg/h infusion	80	1,440	1,440	720	360	3.6
1	18 units/kg/h infusion	80	1,440	(0)	1,440	720	7.2
2	18 units/kg/h infusion	80	1,440	(0)	(0)	1,440	14.4
Approximate amount of unfractionated heparin remaining in circulation →						3,320	33.2
LMWH delivery time (h)	**LMWH dose**	**Patient weight (kg)**	**LMWH dose administered (mg)**	**LMWH remaining within 8 h[a] (mg)**	**LMWH remaining at 8–12 h[a] (mg)**	**LMWH remaining after 12 h (mg)**	**Protamine dose (mg) required to reverse LMWH[c]**
0	1 mg/kg every 12 h	80	80	80	–	–	80
8	(0)	80	–	–	40	–	40
12	(0)	80	–	–	–	≤ 20	0–20

[a]This model assumes a half-life for UFH of 1 h and for LMWH 8 h.
[b]Estimated amounts of UFH remaining at 1 h following initiation of a continuous infusion may be overestimated in this model.
[c]Administer no more than 20 mg of protamine per minute, in divided doses, with no more than 50 mg over any 10-min period.
UFH, unfractionated heparin, LMWH, low-molecular-weight heparin.

GP IIb/IIIa inhibitors, aspirin or fibrinolytic agents [53–55]. Patient-specific risk factors for bleeding include age, gender, renal failure, low body weight, and excessive alcohol consumption [53].

Perioperative anticoagulation must be individualized based on the surgery or procedure and the patient's risks for thrombosis and bleeding. Discontinuing therapeutic doses of heparin 4 hours before surgery and measuring an aPTT is usually sufficient since normal hemostasis is restored in this time frame [16,56,57]. Therapeutic-dose heparin therapy can be restarted 12 hours after major surgery, but should be delayed if evidence of bleeding is present. There is no contraindication to neuraxial techniques in patients receiving twice daily, low-dose UFH subcutaneously, as the risk for developing spinal hematoma appears to be minimal [16,30].

Treatment of UFH-related bleeding includes protamine sulfate, transfusion, and supportive care. Protamine sulfate binds to UFH to form a stable salt, which renders heparin inactive. Protamine dosing is dependent on timing of the last heparin dose. For immediate reversal (< 30 minutes since last heparin dose), 1 mg of protamine is administered for every 100 units of heparin and a followup aPTT can evaluate the reversal response. When UFH is given as a continuous IV infusion, only UFH delivered during the preceding 2 to 2.5 hours should be included in the calculation to determine the protamine dose (Table 110.8) [58]. If the dose of heparin is unknown, the maximal tolerated protamine dose of 50 mg can be slowly administered followed by serial measurements of aPTT. Adverse reactions, such as hypotension and bradycardia, are common. However, reaction severity can be reduced by slowly administering protamine over 1 to 3 minutes. Allergic responses to protamine are more common in patients who have been previously exposed to the drug, but patients can be pretreated with corticosteroids and antihistamines [53,59,60].

Low-Molecular-Weight Heparins

Pharmacology, Pharmacodynamics, and Monitoring

LMWHs are derived from UFH by chemical or enzymatic depolymerization, yielding fragments approximately one-third the molecular weight of UFH. All LMWH molecules contain the active pentasaccharides that catalyze AT inhibition of factor Xa. Because of their smaller size, LMWHs have decreased affinity for plasma proteins and cellular binding sites, resulting in a superior pharmacokinetic profile compared to UFH. LMWHs also have increased bioavailability after subcutaneous injection, renal clearance that is dose-independent, and a longer half-life (17 to 21 hours). LMWHs are administered in fixed doses for thromboprophylaxis or in total body weight-adjusted doses for therapeutic anticoagulation (Table 110.9) [45,61].

With their predictable dose response (peak anti-Xa activity occurs 3 to 5 hours after injection), laboratory monitoring is usually not necessary. Anti-Xa monitoring is optional in high-risk patient populations, specifically renal insufficiency, obesity, and pregnancy. In these cases, anti-Xa plasma levels are drawn 4 hours after administration, and subsequent doses are adjusted to a target range of 0.5 to 1.1 IU per mL [62].

Clinical Indications

LMWHs are suitable replacements for UFH for many indications [63]. LMWHs require fewer injections and produce fewer adverse events. In hospitalized medical patients receiving thromboprophylaxis, LMWH was associated with a lower risk of DVT, fewer injection site hematomas, and no difference in bleeding when compared with UFH [64]. LMWHs have largely replaced intravenous UFH in patients with acute VTE who are able to receive unmonitored anticoagulation in the ambulatory setting. UFH remains the preferred option for ACS patients,

TABLE 110.9

CLINICAL USES OF LOW-MOLECULAR-WEIGHT HEPARINS

Drug	Indications	Dosing, timing, duration	Precautions
Enoxaparin (Lovenox™)	Treatment of VTE	1 mg/kg SC every 12 h OR 1.5 mg/kg SCevery 24 h CrCl < 30 mL/min: 1 mg/kg SC every 24 h	■ Indwelling epidural catheter ■ Recent spinal or ophthalmologic surgery ■ History of recent major bleed (gastrointestinal, intracranial, etc.) ■ Congenital or acquired bleeding disorders ■ History of heparin-induced thrombocytopenia ■ Liver disease ■ Renal impairment (CrCl < 30 mL/min), consider unfractionated heparin ■ Concomitant use of antithrombotic drugs ■ Diabetic retinopathy ■ Uncontrolled hypertension
	Treatment of ACS	30 mg bolus IV followed by 1 mg/kg SC every 12 h WITH tenecteplase CrCl < 30 mL/min: not recommended	
	Prophylaxis/bridge therapy for atrial fibrillation/ cardioversion	1 mg/kg SC every 12 h OR 1.5 mg/kg SC every 24 h CrCl < 30 mL/min: 1 mg/kg SC every 24 h	
	Prophylaxis of VTE in the medically ill or surgical population	40 mg SC every 24 h CrCl < 30 mL/min: 1 mg/kg SC daily	
	Prophylaxis of VTE in the trauma patients	30 mg SC every 12 h OR 40 mg SC every 24 h	
Dalteparin (Fragmin™)	Treatment of VTE	< 56 kg: 10,000 IU daily 57–68 kg: 12,500 IU daily 69–82kg: 15,000 IU daily 83–98 kg: 18,000 IU daily > 99 kg: 18,000 IU daily	
	Treatment of ACS	120 IU/kg SC every 12 h (MAX 10,000 IU/dose)	
	Prophylaxis of VTE after hip or other major surgery (first month)	Initial dose: 2500 IU once Maintenance: 2,500–5,000 IU SC every 24 h	
	Prophylaxis of VTE in the medically ill or surgical population	5,000 IU SC every 24 h	
Tinzaparin (Innohep™)	Treatment of DVT	175 international units anti-Xa/kg SC daily	

ACS, acute coronary syndrome; CrCl, creatinine clearance using Cockcroft–Gault equation; IU, international units; IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.

those who may require an urgent surgical intervention, those with compromised renal function, or those requiring intensive monitoring for other reasons [48].

Complications and Reversal of Effect

Hemorrhage is the major complication of LMWH therapy, with data suggesting lower rates when compared to UFH. Major bleeding is reported to occur in 0% to 3% of patients [53]. Preprocedural thromboembolic risk assessment, bleeding risk assessment, and physician preference will play a role in determining whether LMWH prophylaxis is continued or withheld in the surgical setting. For patients receiving therapeutic LMWH, therapy should be discontinued 12 to 24 hours prior to the procedure, or earlier in patients with renal dysfunction. Therapeutic doses of LMWH should not be restarted for 24 hours after a major procedure or with neuraxial anesthesia [16,30].

In the setting of overdose or hemorrhage, protamine completely reverses the antithrombin activity of LMWH, but only reverses 60% of the antifactor Xa activity. If immediate reversal is warranted within 8 hours of LMWH administration, a protamine dose of 1 mg neutralizes 100 anti-Xa units or 1 mg of LMWH (Table 110.8). Should bleeding continue, a second dose of 0.5 mg of protamine per 100 anti-Xa units may be administered. Smaller protamine doses are required if the LMWH administration interval is beyond 8 hours [65,66].

Heparin-induced thrombocytopenia (HIT) is an immune-mediated, hypercoagulable disorder that results from antibodies formed against the heparin-platelet factor 4 complex. The incidence in critically ill patients ranges from 1% to 5% and is associated with thrombocytopenia and life-threatening thrombosis in approximately 30% to 50% of antibody-positive patients [67]. HIT typically occurs in patients who have been exposed to UFH or LMWH for 5 to 7 days, or even sooner in patients with prior exposure. A 50% decrease in platelet count occurring 4 to 10 days after the initiation of UFH or LMWH therapy or formation of a new thrombus during therapy may be indicative of HIT. Platelet counts should be measured prior to the initiation of UFH or LMWH and monitored every other day for the first 4 to 10 days of therapy. Since heparin alternatives must be used in patients with HIT, direct thrombin inhibitors are the treatment of choice [68,69].

Patients receiving heparin for a period of greater than 1 month are at risk for developing osteoporosis and vertebral

TABLE 110.10

CLINICAL USES OF FONDAPARINUX

Drug	Indications	Dosing, timing, duration	Precautions
Fondaparinux (Arixtra™)	Treatment of VTE Treatment is for 5–9 d; continue treatment until a therapeutic oral anticoagulant effect is established	< 50 kg: 5.0 mg SC daily 50–100 kg: 7.5 mg SC daily > 100 kg: 10 mg SC daily Renal impairment CrCL 50–80 mL/min—25% reduction in total clearance; consider empiric dosage reduction CrCL 30–50 mL/min—40% reduction in total clearance; consider empiric dosage reduction CrCL less than 30 mL/min—contraindicated	■ Indwelling epidural catheter ■ Recent spinal or ophthalmologic surgery ■ History of recent major bleed (gastrointestinal, intracranial, etc.) ■ Congenital or acquired bleeding disorders
	Treatment of STEMI and NSTEMI[a]	2.5 mg SC daily	
	Prophylaxis of VTE in major surgery and acute medically ill[a]	2.5 mg SC daily	

[a]Indicates off-label use of medication.
CrCl, creatinine clearance using Cockcroft–Gault equation; NSTEMI, non ST-elevation myocardial infarction; SC, subcutaneous; STEMI, ST-elevation myocardial infarction; VTE, venous thromboembolism.

fractures. Osteoporosis reportedly occurs less frequently in patients treated with LMWHs as compared to UFH [48].

Fondaparinux

Fondaparinux is a synthetic analog of the naturally occurring pentasaccharide found in heparins. Fondaparinux selectively and irreversibly binds to AT. This results in neutralization of factor Xa, which ultimately inhibits thrombin formation and thrombus development [48].

Pharmacology, Pharmacodynamics, and Monitoring

After subcutaneous administration, fondaparinux has a half-life of 17 to 21 hours in patients with normal renal function. Fondaparinux is excreted in the urine with clearance reduced in patients with renal impairment. As with LMWHs, monitoring of anti-Xa levels is not required during fondaparinux administration (Table 110.10) [48].

Clinical Indications

Fondaparinux is as safe and effective as the heparins for treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and for thromboprophylaxis in surgical and medically ill patients [70–73]. Fondaparinux showed superior efficacy in reducing VTE in patients undergoing knee arthroplasty, hip arthroplasty, and hip fracture surgery [74–76]. In a combined analysis, the overall incidence of major bleeding was statistically higher with fondaparinux (2.7%) compared with LMWH (1.7%) [77]. However, the incidence of clinically relevant bleeding, defined as bleeding leading to death, reoperation, or occurring in a critical organ, did not differ between the agents. Differences in efficacy and safety outcomes could be related to the timing of perioperative drug administration. Fondaparinux given less than 6 hours after surgery has been associated with an increased frequency of major bleeding [77]. Fondaparinux may be an option for thromboprophylaxis in the setting of HIT but conclusive data are not available [78].

Complications and Reversal of Effect

Fondaparinux is contraindicated in patients with severe renal impairment (calculated creatinine clearance < 30 mL per minute) and should not be used for VTE prophylaxis in patients weighing less than 50 kg. No antidote exists for fondaparinux-related hemorrhage and reversal is further complicated by its prolonged half-life [79]. Recombinant factor VIIa (rVIIa) reverses the coagulation defect induced by fondaparinux, but the clinical utility is unknown [80,81]. With a short half-life (2 to 3 hours), rVIIa may require repeat dosing. The use of fondaparinux and neuraxial anesthesia or analgesia should follow the conditions used in clinical trials as closely as possible [30].

Direct Thrombin Inhibitors

The direct thrombin inhibitors (DTIs) are lepirudin, bivalirudin, and argatroban. They exert their antithrombotic effect by binding to the active site of thrombin and inhibiting thrombin-catalyzed reactions. This prevents fibrin formation, activation of coagulant factors V, VIII, XIII, protein C, and platelet aggregation [82].

Pharmacology, Pharmacodynamics, and Monitoring

Lepirudin (*r*-hirudin) is a recombinant derivative of hirudin, produced from leech salivary glands. Bivalirudin is the synthetic analog of r-hirudin. Argatroban, derived from the amino acid arginine, is a small synthetic molecule. The DTIs differ in their pharmacokinetic parameters (Table 110.11) [82]. Lepirudin is eliminated through renal clearance, argatroban by hepatic metabolism, and bivalirudin by proteolytic cleavage in the plasma. Bivalirudin has the shortest half-life, making it a particularly useful agent in the procedural or periprocedural period. DTI selection is predicated on patient-specific characteristics such as hemodynamic stability, hepatic function, and renal function. Critically ill patients typically require lower doses than recommended by the manufacturer [82,83]. DTIs are monitored using aPTT (Table 110.12). The aPTT level should be measured every 6 hours until the patient has sustainable therapeutic levels, then the monitoring frequency can be extended [69].

Clinical Indications

Lepirudin and argatroban significantly reduce the rates of thromboembolic complications in patients with HIT [84,85].

TABLE 110.11

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF DIRECT THROMBIN INHIBITORS

Feature	Lepirudin	Argatroban	Bivalirudin
Molecular weight (Da)	6,979	526	2,180
FDA-approved indication	Management of HIT	Management of HIT, or use in patients with HIT who are undergoing PCI	Use in patients with or at risk for HIT or HITTS who are undergoing PCI
Primary elimination route	Renal	Hepatic	Enzymatic
Elimination half-life	1.3 h	39–51 min	10–24 min
Fraction eliminated unchanged by kidney (%)	35	16	20
Laboratory test to monitor	aPTT, ECT	aPTT, ECT	aPTT, ACT, ECT
Target range	aPTT: 1.5–2.5 × control	aPTT: 1.5–3 × control	aPTT: 1.5–2.5 × control
Effects on INR	Minimal	Moderate to clinically significant	Minimal to moderate

ACT, activated clotting time; aPTT, activated partial thromboplastin time; Da, dalton; ECT, ecarin clotting time; FDA, Food and Drug Administration; HIT, heparin-induced thrombocytopenia; HITTS, HIT with thrombosis syndrome; INR, international normalized ratio; PCI, percutaneous coronary intervention.

Bivalirudin has been safely used in critically ill HIT patients [86]. Argatroban and bivalirudin are indicated for prophylaxis of thrombosis in patients with, or at risk for, HIT undergoing PCI. Bivalirudin is also indicated in the treatment of patients undergoing PCI as well as those with unstable angina/non-ST segment elevation myocardial infarction undergoing PCI (see Table 110.12) [87].

Complications and Reversal of Effect

No specific reversal agent is available for DTI-induced hemorrhage.

For lepirudin, hemofiltration may be an alternative in the setting of life-threatening hemorrhage. Anecdotally, rVIIa has been reported to be useful as well [88]. DTIs can produce elevation in the international normalized ratio (INR), an effect that is most pronounced with argatroban, and magnified when coadministered with warfarin. This laboratory interaction has misled clinicians to discontinue argatroban therapy prematurely, predisposing patients to venous limb gangrene [78]. With concurrent administration, the argatroban infusion should be stopped and the INR measured 4 to 6 hours. If the INR is within therapeutic range on warfarin alone, warfarin monotherapy can be continued, otherwise argatroban therapy should be resumed.

Oral Anticoagulants—Vitamin K Antagonists

Warfarin, a vitamin K antagonist (VKA), inhibits the enzyme vitamin K epoxide reductase complex (VKORC), which converts vitamin K to an active form. The absence of vitamin K reduces the hepatic production of functional coagulation factors II (thrombin), VII, IX, and X and the regulatory anticoagulant proteins C, S, and Z. Since thrombin has a longer half-life (60 to 72 hours) compared to the other factors (6 to 24 hours), at least 6 days of warfarin treatment is required for an antithrombotic effect [89].

Warfarin is extensively metabolized by the CYP450 isoenzyme system including CYP2C9, CYP1A1, CYP1A2, and CYP3A4. Several genetic polymorphisms have been identified with CYP2C9 and VKORC that may influence warfarin clearance and dose sensitivity [90,91].

In critically ill patients, alterations in coagulation factors, caused by reduced dietary vitamin K intake, hypoalbuminemia, antibiotic administration, acute hepatic injury, or hypermetabolic states, will impact the effects of warfarin [90,91]. Furthermore, drug interactions alter warfarin absorption, clearance, and plasma protein binding. The interactions could have either synergistic or antagonistic effects [89].

Warfarin's anticoagulant effect is measured using the INR [92]. The INR uses the international sensitivity index of the local thromboplastin reagent to standardize the laboratory result. The INR target range will vary based on indication and the patient's risk for thromboembolic and bleeding complications (see Table 110.13). Nomogram-based warfarin dosing is considered safer and more effective for reaching target INR goals. To prevent excessive anticoagulation, loading doses are avoided and low doses are employed for the elderly [93]. Frequent INR monitoring is necessary during initiation of therapy until steady state is reached.

Clinical Indications

Warfarin is effective for primary and secondary prevention of venous thromboembolism, for prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, and for prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction [89,94–96].

Complications and Reversal of Effect

Treatment with warfarin increases the risk of major bleeding by 0.3% to 0.5% per year and the risk of intracerebral hemorrhage by approximately 0.2% per year compared to controls [53]. Important risk factors for hemorrhage include anticoagulant intensity, time within therapeutic range, and patient age. Higher goal INR (INR > 3) has been directly associated with increased hemorrhage rates. Elevated INR can be managed by withholding or decreasing warfarin doses. In patients experiencing or at risk of bleeding, vitamin K administration will reverse the anticoagulant effects of warfarin. Vitamin K is given orally or parenterally. Oral vitamin K normalizes supratherapeutic INRs more rapidly than subcutaneous vitamin K [97]. Intravenous vitamin K corrects excessive warfarin anticoagulation quicker and more completely than subcutaneous administration [98].

For patients with an INR > 5.0 but < 9.0 and no significant bleeding, the next two doses of warfarin should be held, and low dose (1 to 2.5 mg) oral vitamin K administered. For patients with an INR > 9.0, the vitamin K dose can be increased to 2.5 to 5 mg [89].

In the setting of serious or life-threatening hemorrhage, warfarin should be held and vitamin K 10 mg administered by slow IV infusion. The supplementation of coagulation factors with

TABLE 110.12

CLINICAL USES OF DIRECT THROMBIN INHIBITORS

Drug	Indications	Dosing, timing, duration	Precautions
Bivalirudin (Angiomax™)	PCI (with glycoprotein IIB/IIIA inhibitor)	0.75 mg/kg IV bolus dose, followed by an infusion of 1.75 mg/kg/h for the duration of the procedure CrCl less than 30 mL/min, a reduction of initial infusion rate to 1 mg/kg/h should be considered; no bolus dose reduction is necessary	■ Indwelling epidural catheter ■ Recent major, spinal or ophthalmologic surgery, or cerebrovascular accident ■ History of recent major bleed (gastrointestinal, intracranial, etc.) ■ Congenital or acquired bleeding disorders ■ Repeat lepirudin courses may require more frequent monitoring due to antibody formation ■ Hepatic impairment (argatroban) ■ Renal dysfunction (bivalirudin and lepirudin)
	Treatment of ACS[a]	Initial IV bolus dose of 0.1 mg/kg, followed by 0.25 mg/kg/h. Titration to aPTT 1.5–2 times control	
	Treatment and prophylaxis of HITT[a]	0.1–0.2 mg/kg/h, titration to aPTT 1.5–2 times control	
Argatroban	Treatment and prophylaxis of HITT	0.5–1.2 µg/kg/min continuous IV infusion to start titration to goal aPTT between 50 and 85 s. Begin VKA therapy, measure INR daily. Stop argatroban when INR > 4. Repeat INR in 4–6 h, if INR is below desired range then resume argatroban infusion	
	Treatment of ACS	Bolus: 100 µg/kg Initial infusion: 1–3 µg/kg/min for 6–72 h; maintain aPTT between 50 and 85 s	
Lepirudin (Refludan™)	Treatment and prophylaxis of HITT ■ aPTT ratio target: between 1.5 and 2.5; begin monitoring aPTT 4 h after initiation of infusion and daily thereafter; recheck aPTT 4 h after any dosage changes ■ aPTT greater than 2.5: discontinue infusion for 2 h, decrease infusion rate by 50% when reinstated ■ aPTT less than 1.5: increase infusion rate in 20% increments until target aPTT is achieved	Bolus: 0.4 mg/kg IV (up to 44 mg) Initial infusion: 0.05–0.15 mg/kg/h (up to 16.5 mg/h) for 2–10 d, adjust infusion rate according to aPTT ratio Renal impairment CrCl < 60 mL/min): Bolus: 0.2 mg/kg IV Initial infusion: 0.001–0.01 mg/kg/h (up to 16.5 mg/h) for 2–10 d, adjust infusion rate according to aPTT ratio	

[a] Indicates off-label use of medication.
ACS, acute coronary syndrome; ACT, activated clotting time; aPTT, activated partial thromboplastin time; CBC, complete blood count; CrCl, creatinine clearance using Cockcroft–Gault equation; HITT, heparin-induced thrombocytopenia and thrombosis; INR, international normalized ratio; IV, intravenous; PCI, percutaneous coronary intervention; PT, prothrombin time; VKA, vitamin K antagonist.

fresh frozen plasma (FFP) or prothrombin complex concentrate may be more effective in cases where immediate reversal of the INR is necessary [98]. Recombinant factor VIIa may be beneficial in patients with refractory bleeding in the setting of elevated INRs, or those requiring an invasive procedure [89,99–101].

Nonhemorrhagic adverse events of warfarin include acute skin necrosis and limb gangrene. These complications are typically observed on the third to eighth day of therapy [89].

In patients scheduled for surgery, warfarin may be continued, interrupted for approximately 5 days, or replaced with short-term parenteral or bridge therapy depending on the patient's risk for venous or arterial thromboembolism. Warfarin is resumed after surgery. Most bridging regimens have been developed from observational studies since there is not a standardized definition of bridging [101,102].

For warfarin-treated patients receiving neuraxial anesthesia with an indwelling catheter, the catheter should be removed when the INR is less than 1.5. Patients with a low risk of bleeding may undergo surgery with an INR of 1.3 to 1.5 [30,101].

TABLE 110.13

CLINICAL USES OF WARFARIN

Drug	Indications	Dosing, timing, duration	Precautions
Warfarin (Coumadin™)	Treatment of VTE	Initial dosing: 2.5–10 mg every 24 h (see precautions) titrated to range INR: 2.0–3.0; target of 2.5	■ Lower initial dosing (< 5 mg may be warranted in patients who are debilitated, or are taking medications known to increase sensitivity to warfarin ■ Cerebrovascular disease ■ Coronary disease ■ CYP2C9 and VKORC1 genetic variation ■ Moderate to severe hypertension ■ Malignancy ■ Renal impairment ■ Recent trauma ■ Malignancy ■ Collagen vascular disease ■ Conditions that increase risk of hemorrhage, necrosis, and/or gangrene, pre-existing ■ Congestive heart failure ■ Excessive dietary vitamin K ■ Vitamin K deficiency ■ Elderly or debilitated patients (lower dosing may be required) ■ Hepatic impairment ■ Hyperthyroidism/hypothyroidism ■ Epidural catheters ■ Infectious diseases or disturbances of intestinal flora, such as sprue or antibiotic therapy ■ Poor nutritional state ■ Protein C deficiency ■ Heparin-induced thrombocytopenia
	Atrial fibrillation	Initial dosing: 2.5–10 mg every 24 h (see precautions) titrated to range INR: 2.0–3.0; target of 2.5	
	Post MI	Initial dosing: 2.5–10 mg every 24 h (see precautions) titrated to range INR 2.0–3.0; target of 2.5	
	Mechanical valve in the atrial position	Initial dosing: 2.5–5 mg every 24 h (see precautions) titrated to range INR 2.0–3.0; target of 2.5	
	Mechanical valve in the mitral position	Initial dosing: 2.5–5 mg every 24 h (see precautions) titrated to range INR 2.5–3.5; target of 3.0	
	Mechanical valve in both the atrial and mitral position	Initial dosing: 2.5–5 mg every 24 h (see precautions) titrated to target INR 2.5–3.5; target of 3.0	
	Bioprosthetic valve in the mitral position	Initial dosing: 2.5–5 mg every 24 h (see precautions) titrated to target INR 2.0–3.0; target of 2.5 for 3 months	

[a]Indicates off label use of medication.
INR, international normalized ratio; MI, myocardial infarction; VTE, venous thromboembolism.

FIBRINOLYTIC THERAPY

Overview of Fibrinolytic Pharmacotherapy

Fibrinolytic agents have been used clinically since the 1950s when streptokinase was shown to be effective in dissolving occlusive thrombi.

Pharmacology, Pharmacodynamics, and Monitoring

Fibrinolytic agents promote the conversion of plasminogen to plasmin, which subsequently causes the degradation of fibrin clots [103]. Streptokinase and urokinase are naturally occurring first-generation fibrinolytic agents [104]. Recombinant tissue plasminogen activator (rt-PA) is a second-generation fibrinolytic that causes less overall systemic depletion of fibrinogen

TABLE 110.14

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF FIBRINOLYTICS

	Streptokinase	Urokinase	Alteplase	Reteplase	Tenecteplase
	First-generation		Second-generation	Third-generation	
Source	Group C β-hemolytic strep	Synthesized from urine or kidney cell tissue	Recombinant DNA technology	Recombinant DNA technology	Recombinant DNA technology
Molecular weight (Da)	47,000	Variable	70,000	39,000	70,000
Administration	Continuous infusion	Continuous infusion	Rapid continuous infusion	Sequential bolus	Single bolus
Half-life	20–80 min	15–20 min	5 min	15–18 min	20 min

Da, dalton; DNA, deoxyribonucleic acid;

TABLE 110.15

CLINICAL USES OF FIBRINOLYTICS

Drug	Indications	Dosing, timing, duration	Precautions
Alteplase (Activase™ and Cathflo Activase™)	Acute myocardial infarction (accelerated infusion)	>67 kg 15 mg IV bolus, followed by 50 mg infusion over 30 min, then 35 mg infusion over 60 min (total = 100 mg) ≤67 kg 15 mg IV bolus, followed by 0.75 mg/kg infusion over 30 min (max 50 mg), then 0.5 mg/kg over 60 min (max 35 mg)	■ Recent major or minor surgery (within 10 d) ■ Cerebrovascular diseases ■ Recent gastrointestinal or genitourinary bleeding ■ Recent trauma ■ Hypertension: systolic BP greater than or equal to 175–180 mmHg and/or diastolic BP greater than or equal to 110 mmHg ■ Left heart thrombus ■ Acute pericarditis ■ Subacute bacterial endocarditis ■ Hemostatic defects ■ Severe hepatic or renal dysfunction ■ Pregnancy ■ Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions ■ Septic thrombophlebitis or occluded arteriovenous cannula at a seriously infected site ■ Advanced age
	Pulmonary embolism	Routine administration for PE (noncardiac arrest): 100 mg IV administered over 120 min During cardiopulmonary resuscitation: 50 mg IV single dose administered over 5 min	
	Acute ischemic stroke (within 3 h of symptom onset)	0.9 mg/kg IV (not to exceed 90 mg total dose) infused over 60 min with 10% of the total dose administered as an initial intravenous bolus over 1 min	
	Arterial thrombosis	Catheter-directed administration: 1.5 mg/h by transcatheter intra-arterial infusion until lysis of thrombus	
	Central venous catheter occlusion	Weight >30 kg 2 mg/2 mL Weight >10 kg but <30 kg 110% of the internal lumen volume, not to exceed 2 mg/2 mL	
Reteplase (Retavase™)	Acute myocardial infarction	10 unit IV bolus, two doses given 30 min apart	■ Patients receiving oral anticoagulants ■ Known or suspected infection in the catheter during use for catheter clearance
	Central venous catheter occlusion[a]	0.4 units/2 mL	
Tenecteplase (TNKase™)	Acute myocardial infarction	<60 kg: 30 mg dose ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg Single IV bolus over 5 s	■ Severe neurological deficit (NIHSS >22) (ischemic stroke) ■ Patients with major early infarct signs on computerized cranial tomography (ischemic stoke) ■ History of streptococcal infection within 5 d–12 mo (streptokinase)
Streptokinase (Streptase™)	Acute myocardial infarction	1.5 million IU over 60 min	■ Previous streptokinase administration (within 5 d–12 mo)
	Pulmonary embolism	250,000 IU IV over 30 min, then 100,000 IU/h for 24 h	
	Deep venous thrombosis	250,000 IU IV over 30 min, then 100,000 IU/h for 72 h	
	Arterial thrombosis	250,000 IU IV over 30 min, then 100,000 IU/h for 24 h	
Urokinase (Abbokinase™ or Kinlytic™)	Pulmonary embolism	Loading dose: 4,400 IU/kg IV over 10 min, then 4,400 IU/kg/h IV for 12 h	
	Central venous catheter occlusion[a]	5,000 IU, fill volume of catheter for 1–4 h. May repeat with 10,000 IU in catheter if first dose fails.	

[a]Indicates off-label use of medication.
BP, blood pressure; IU, international units; IV, intravenous; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale.

and plasminogen compared with streptokinase and urokinase. The half-life of rt-PA is less than 5 minutes when administered as a bolus followed by rapid continuous infusion. Third-generation fibrinolytic agents are synthetic agents with increased fibrin specificity compared to first-generation fibrinolytics and extended half-lives compared to rt-PA [104]. Reteplase is administered in sequential intravenous bolus doses while tenecteplase is administered as a single bolus (Table 110.14). The beneficial properties of the newer agents continue to be evaluated in clinical trials.

Clinical Indications

Fibrinolytic therapy is administered to patients with acute ischemic stroke, venous thromboembolism, acute myocardial

TABLE 110.16

SELECTED EVIDENCE-BASED CLINICAL TRIALS OR META-ANALYSES RELEVANT TO THE CARE OF INTENSIVE CARE UNIT PATIENTS

Indication	Comparison	Result	Reference
Antiplatelet therapies	Meta-analysis of 2,930 patients with cardiovascular disease treated with aspirin regimens ranging from 75 to 325 mg daily Double-blind trial comparing ticagrelor (180-mg loading dose, 90 mg twice daily) versus clopidogrel (300–600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome.	Overall, 28% of patients were classified as aspirin resistant. A cardiovascular-related event occurred in 41% of patients, an acute coronary syndrome in 40%, and death in 6%. Aspirin-resistant patients are at a greater risk of clinically important cardiovascular morbidity. Over 12 mo the composite of death from vascular causes, myocardial infarction, or stroke occurred in 9.8% ticagrelor patients vs 11.7% of those receiving clopidogrel. There were no significant differences in the rates of major bleeding (11.6% vs 11.2%).	[14] [25]
Antithrombotic therapies Thromboprophylaxis in medically ill patients Treatment of acute pulmonary embolism (MATISSE PE) Reversal of warfarin anticoagulant effect with vitamin K	Meta-analysis comparing the incidence of DVT and PE in hospitalized medically ill patients receiving thromboprophylaxis with UFH twice daily, to UFH tree times daily and to LMWH. Open-label trial comparing fondaparinux to aPTT-monitored intravenous UFH for the initial treatment of hemodynamically stable patients with PE. Open-label trial comparing vitamin K subcutaneous vs intravenous administration in patients with an INR > 6.0 without active bleeding.	UFH dosage of 5,000 units three times daily was more effective in preventing DVT than UFH 5,000 units twice daily. LMWH was associated with a lower risk of DVT and injection site hematoma but no difference was seen in the risk of bleeding or thrombocytopenia. The 3-mo incidence of the composite end point of symptomatic, recurrent PE (nonfatal or fatal) and new or recurrent deep-vein thrombosis was similar in fondaparinux-treated patients (3.8%) and those assigned to UFH (5.0%). Major bleeding occurred in 1.3% of patients treated with fondaparinux and 1.1% of those treated with unfractionated heparin. Intravenous vitamin K corrects excessive warfarin anticoagulation quicker and more completely than subcutaneous administration.	[64] [71] [98]
Thrombolytic therapies Treatment of acute ischemic stroke Treatment of submassive pulmonary embolism Treatment of acute myocardial infarction	Double-blind trial comparing the safety and efficacy of alteplase administered between 3 and 4.5 h after the onset of a stroke. The primary end point was disability. Meta-analysis of randomized trials comparing thrombolytic therapy with UFH in patients with acute pulmonary embolism. Open-label trial comparing the efficacy and safety of tenecteplase plus enoxaparin or abciximab with that of tenecteplase plus weight-adjusted unfractionated heparin in patients with acute MI.	More patients had a favorable outcome at 90 d with alteplase (52%) than with placebo (45%) when measured using the modified Rankin scale. The incidence of intracranial hemorrhage was higher with alteplase than with placebo. Mortality did not differ significantly between the groups. Thrombolytic therapy was associated with a nonsignificant reduction in recurrent pulmonary embolism, death, and a nonsignificant increase in major bleeding when compared to UFH. When thrombolytic therapy was compared with UFH in patients with major (hemodynamically unstable) PE, thrombolysis was associated with a significant reduction in recurrent PE or death. There were significantly fewer efficacy (composites of 30-d mortality, in-hospital reinfarction, or in-hospital refractory ischemia) and efficacy plus safety end points (in-hospital intracranial hemorrhage or in-hospital major bleeding complications) in the enoxaparin and abciximab groups than in the UFH group.	[108] [111] [113]

MATISSE PE, Mondial Assessment of Thromboembolism Treatment Initiated by Synthetic Pentasaccharide with Symptomatic Endpoints—Pulmonary Embolism; UFH, unfractionated heparin; DVT, deep venous thrombosis; LMWH, low-molecular-weight heparin; aPPT, activated partial prothrombin time; MI, myocardial infarction; PE, pulmonary embolism.

infarction, peripheral arterial occlusion, and in those patients requiring venous catheter maintenance (Table 110.15).

The goal of fibrinolytic therapy in acute ischemic stroke is to recanalize vessels and rapidly restore oxygenation to ischemic but salvageable brain tissue. rt-PA has been shown to improve long-term neurological recovery [105,106]. Pooled analysis of six trials comparing rt-PA to placebo showed that treatment benefit increased as time to start of therapy decreased [107]. While recent guidelines recommend intravenous rt-PA treatment within 3 hours of symptom onset, emerging evidence suggests additional benefit without increased bleeding risk in patients treated between 3 and 4.5 hours [108]. The intra-arterial route is recommended for patients with angiographically demonstrated middle cerebral artery occlusion and without major early infarct signs on CT or MRI scan, who can be treated within 6 hours of symptom onset in a center with the appropriate expertise [109]. Streptokinase is not recommended for acute ischemic stroke due to increased mortality and symptomatic intracranial hemorrhage [109]. Anticoagulants and antiplatelet agents should be held for 24 hours, or until coagulation parameters have returned to normal, after treatment with intravenous rt-PA therapy.

Fibrinolytic therapy is indicated for treatment of acute massive PE to accelerate lysis, provide hemodynamic improvement, and reverse cardiogenic shock. Fibrinolytic use is controversial in patients with submassive PE. Treatment is based on risk stratification of PE severity, bleeding risk, and prognosis [110]. A meta-analysis comparing fibrinolytic therapy with heparin alone for initial treatment, however, showed no benefit of fibrinolytic therapy in decreasing recurrent PE or death [111] (Table 110.16).

In centers with expertise, catheter-direct fibrinolytic therapy is a management option for treatment of acute DVT and may reduce long-term complications of postthrombotic syndrome [112].

The goal of therapy for patients presenting with ST-elevation myocardial infarction is rapid reperfusion. For patients presenting to centers without PCI capabilities, or timely transfer to those facilities, fibrinolytic therapy is recommended within 30 minutes of arrival of medical contact or within 30 minutes of hospital arrival if the emergency medical service does not have fibrinolytic capabilities. Fibrinolytic agents have been combined with various anticoagulants and antiplatelet agents to improve outcomes and reduce bleeding [113–115].

A clear role for fibrinolytic therapy, compared with surgical revascularization, for acute limb ischemia has yet to be defined. There is wide variation in fibrinolytic agents employed, doses studied, patient populations, and endpoints of therapy. The greatest benefit has been shown for patients presenting with acute ischemia < 14 days who are at low risk for irreversible ischemia [116].

A common use for fibrinolytic agents is to clear thrombotic occlusions within central venous and dialysis catheters. This therapy is both effective and safe since little to no active drug reaches the systemic circulation [117].

Complications and Reversal of Effect

Because of its derivation from *Streptococcus*, patients may have preformed antibodies to streptokinase from prior streptococcal infections. Adverse drug events include allergic reactions, anaphylaxis, and fever.

Bleeding is the most common and severe complication of fibrinolytic therapy. The most common areas of bleeding are the gastrointestinal and genitourinary tracts as well as sites of interrupted vascular integrity, including catheter access sites, gingiva, and skin [118]. Symptomatic intracerebral hemorrhage rates range between 0.5% and 11% of patients treated with fibrinolytic therapy [119]. A review of six randomized controlled trials of rt-PA for patients with ischemic stroke found an intracerebral hemorrhage rate of 5.9% compared with 1.1% in the placebo groups [107]. Various risk factors for hemorrhage have been identified, but application to clinical practice is limited [120].

Patients receiving fibrinolytic therapy should be closely monitored for intracerebral hemorrhage. Intracerebral hemorrhage should be suspected in patients with sudden focal neurological deterioration (over minutes to hours), decreased level of consciousness, new-onset headache, nausea, vomiting, or acute increases in blood pressure during and within 24 hours of fibrinolytic treatment. Prompt treatment should ensue with replacement of coagulation factors, platelets, FFP, red blood cells, and aminocaproic acid.

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CHAPTER 111 ■ DIAGNOSIS AND MANAGEMENT OF PROTHROMBOTIC DISORDERS IN THE INTENSIVE CARE UNIT

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INTRODUCTION

Arterial and venous thromboembolism are among the most common causes of hospitalization in the United States [1,2]. Given the severity of illness of patients in the intensive care unit (ICU), critical care physicians are likely to manage patients with prothrombotic conditions. In this chapter, we will review the regulation of normal hemostasis (which is required to prevent excessive activity of platelets and/or coagulation factors) and the biology, diagnosis and management of selected prothrombotic disorders in the critical care setting.

Prophylaxis and the general approach to treatment of venous thromboembolism (VTE) are discussed in Chapter 52, "Venous Thromboembolism: Pulmonary Embolism and Deep Venous Thrombosis."

REGULATION OF NORMAL HEMOSTASIS

Hemostasis maintains the integrity of the closed circulatory system after vascular injury. A tenuous balance of prothrombotic (i.e., platelets, coagulation proteins) and endogenous antithrombotic (i.e., antithrombin, nitric oxide) mechanisms ensures hemostasis without pathologic thrombosis. Disruptions of this balance are common in critically ill patients and can lead to clinically significant bleeding or thrombosis. Additional information regarding the normal control of bleeding is present in Chapter 108, "Disorders of Hemostasis in Critically Ill Patients."

The potentially prothrombotic activity of coagulation factors and platelets, however, is opposed by negative regulators of hemostasis. Platelet activation is inhibited by endothelial-derived nitric oxide, prostacyclin, and the ectonucleotidase CD39, which together antagonize platelet activation. The tissue factor pathway is inhibited by tissue factor pathway inhibitor (TFPI). TFPI is synthesized by the endothelium and binds to factor Xa and inhibits its function as well as the activation of factor X by the tissue factor/factor VIIa complex. Since its concentrations increase dramatically with heparin administration, TFPI probably contributes to the antithrombotic efficacy of unfractionated and low-molecular-weight heparin (LMWH) [3,4].

Antithrombin (AT) (formerly antithrombin III) is a liver-derived serine protease inhibitor that inhibits factors XIIa, XIa, IXa, and, in particular, Xa and thrombin by binding to their active sites. Heparin accelerates this reaction to several thousand-fold, thus explaining its potent anticoagulant activity. Protein C (PC) is a liver-derived, vitamin K–dependent protease that is activated on the surface of intact endothelium by thrombin bound to thrombomodulin. This activation event is enhanced by the presence of endothelial PC receptor. Activated protein C (APC) when complexed with its cofactor, protein S (PS), on phospholipid-rich surfaces catalyzes the inactivation of activated forms of factors V and VIII (also known as factor Va and factor VIIIa). PS is a liver-derived, vitamin K–dependent protein that binds to the APC and accelerates its inactivation of factors Va and VIIIa. It exists in the plasma in an active free form that can complex with PC and an inactive form bound to C4b-binding protein [5].

Further regulation of the coagulation cascade is provided by the fibrinolytic system, whose components include plasminogen, tissue plasminogen activator (TPA), plasminogen activator inhibitor I and II, α_2-antiplasmin, and thrombin activatable fibrinolysis inhibitor (TAFI). Plasminogen is a liver-synthesized plasma protein that is converted to plasmin on activation by TPA. Plasmin cleaves fibrin and is principally responsible for clot dissolution and remodeling in the intravascular compartment. Activation of plasminogen is opposed by plasminogen activator inhibitors I and II which inhibit TPA from activating plasminogen. α_2-Antiplasmin is synthesized in the liver and binds to plasmin and prevents it from digesting fibrin clot. TAFI is a carboxypeptidase that is activated by the thrombin–thrombomodulin complex. It removes C-terminal lysine residues from partially digested fibrin clot, thereby downregulating the binding of additional plasminogen to the fibrin clot and thus slowing fibrinolysis [6].

THROMBOPHILIC DISORDERS

Thrombophilic disorders are inherited or acquired conditions that variably increase the risk of venous or arterial thromboembolism depending on the particular alteration and the severity of its impact on the hemostatic mechanism. From a practical diagnostic standpoint, it is most useful to divide these disorders into conditions that are associated with venous or arterial thromboembolism (Table 111.1). A more detailed description of each thrombophilic state follows below along with the appropriate approach to diagnosis.

Factor V Leiden

Factor V Leiden (FVL) is the most common inherited thrombophilic condition affecting approximately 5% of Caucasian European Americans, 2% of Hispanic Americans, 1% of African Americans and Native Americans, and 0.5% of Asian Americans [7]. FVL refers to a single base change (Arg506Gln) in the factor V gene (G1691A) that eliminates the first and most important of three APC cleavage sites. The mutation slows down the inactivation of factor Va by APC leading to more thrombin generation. FVL heterozygosity is associated

TABLE 111.1

INHERITED AND ACQUIRED PROTHROMBOTIC CONDITIONS

Venous thromboembolism	Arterial thromboembolism
Inherited	Inherited
Factor V Leiden	Hyperhomocysteinemia
Prothrombin gene mutation	Dysfibrinogenemia
Antithrombin (III) deficiency	
Protein C deficiency	
Protein S deficiency	
Elevated factor VIII activity	
Elevated factor IX level	
Elevated factor XI level	
Hyperhomocysteinemia	
Dysfibrinogenemia	
Acquired	Acquired
Antiphospholipid syndrome	Antiphospholipid syndrome
Heparin-induced thrombocytopenia	Heparin-induced thrombocytopenia
Cancer	Cancer
Surgery	Surgery
Trauma	Trauma
Pregnancy/postpartum	Inflammation
Central venous catheters	
Vena cava filters	
Immobilization	
Infection/inflammation	
Cardiopulmonary failure	
Exogenous estrogens	

with a 5-fold increased risk of VTE, whereas homozygosity increases this risk by at least 10-fold [8]. FVL does not appear to be associated with an increased risk of arterial thromboembolism [9]. FVL heterozygosity and homozygosity increase the risk of recurrent VTE modestly by 1.56-fold (95% confidence interval [CI], 1.14 to 2.12) and 2.65-fold (95% CI, 1.18 to 5.97), respectively [10]. Diagnosis of FVL relies on a functional screening assay, the APC resistance assay, and confirmatory DNA-based testing.

The Prothrombin G20210A Mutation

The prothrombin gene mutation G20210A (PGM) is present in 1.1% of non-Hispanic Whites and Mexican Americans and in 0.3% of African Americans [11]. It is associated with a 30% increase in prothrombin levels in heterozygotes resulting in a 2.8-fold increased risk of VTE [12]. Homozygosity for the FII mutation is rare, so reliable risk estimates are not available. The PGM does not appear to increase the risk of arterial thromboembolism or recurrent VTE [10,13]. Diagnosis of the PGM is based on DNA testing of peripheral blood.

Compound Heterozygotes for the FVL and FII Mutations

Given the relatively high frequency of FVL and the PGM in the population, double heterozygotes for these mutations are occasionally identified. Compound heterozygosity for both FVL and the PGM is associated with a 20-fold increased risk for first-ever VTE and a 4.8-fold risk for recurrent VTE (95% CI, 0.50 to 46.3) [8,10].

Protein C Deficiency

PC is an important endogenous anticoagulant protein that inactivates factors Va and VIIIa. Heterozygous PC deficiency affects 0.2% of the general population and 3.2% of unselected patients with their first episode of VTE [14]. It is associated with a sevenfold increased risk of VTE [15,16]. Homozygous PC deficiency is a rare thrombophilic syndrome that produces life-threatening thrombotic complications shortly after birth, a condition called *neonatal purpura fulminans*. PC deficiency may result from mutations that produce quantitative (type I deficiency) or qualitative (type II) defects. Therefore, accurate diagnostic testing should include both PC activity and antigen levels. Acquired causes of PC deficiency include disseminated intravascular coagulation/acute thrombosis, vitamin K deficiency, vitamin K antagonist (VKA) therapy (i.e., warfarin), and liver disease. Therefore, diagnostic testing should be performed in the absence of these conditions to ensure that laboratory results are interpretable [17].

Protein S Deficiency

PS is the nonenzymatic cofactor for activated PC. PS circulates in two forms: approximately 60% is bound to C4b binding protein, while the remaining 40% is free. Only free PS has cofactor activity. The incidence of PS deficiency is estimated to be 0.03% to 0.13%. PS deficiency affects 7.3% of unselected patients with venous thrombosis [14,18]. PS deficiency is associated with an eightfold increased risk of VTE [15] and may be a risk factor for arterial thromboembolism [19,20].

Deficiency of PS may by quantitative (type I deficiency) or qualitative (type II). An additional type of deficiency (type III) can be acquired during pregnancy, inflammatory states, and estrogen therapy, which increase C4b binding protein levels leading to reduced free PS. Other acquired causes of PS deficiency include vitamin K deficiency, VKA therapy (i.e., warfarin), acute thrombosis, and liver disease. For accurate diagnosis of PS deficiency, all three tests including PS activity, total PS antigen and free PS antigen should be checked in the absence of conditions associated with acquired PS deficiency [18].

Antithrombin (III) Deficiency

AT inhibits serine protease coagulation factors by binding to the active site of the target protease and forming an inactive complex. Heterozygous type I AT deficiency is rare, affecting 1 in 2,000 in the population. It is associated with an 8- to 10-fold increased risk of thrombosis and is present in 1% to 2% of patients with thrombosis [21]. AT deficiency does not increase the risk of arterial thromboembolism [19,20].

Deficiency of AT may by quantitative (type I deficiency) or qualitative (type II). Complete AT deficiency is incompatible with life. The diagnosis of AT deficiency is made by measuring AT activity and antigen levels. Acquired AT deficiency may occur in acute thrombosis, disseminated intravascular coagulation, and during heparin therapy. Artifactual increases in AT can be seen during therapy with VKAs (e.g., warfarin) [21].

Dysfibrinogenemia

Dysfibrinogenemia is a rare inherited thrombophilic state caused by mutations in the Aα, Bβ, or γ fibrinogen genes and affects fewer than 1% of patients with venous thrombosis. Acquired dysfibrinogenemia is associated with chronic liver disease and cirrhosis as well as liver cancers and renal cell

carcinoma. Approximately one third of cases of dysfibrinogenemia are complicated by thrombosis (venous more commonly than arterial), possibly because of reduced thrombin binding or inhibition of fibrinolysis. Diagnosis of dysfibrinogenemia is made by measuring fibrinogen function (e.g., Clauss fibrinogen assay) as well as fibrinogen antigen. Typically, the fibrinogen activity level is much lower than the fibrinogen antigen level [22,23].

Hyperhomocysteinemia

Homocysteine is a thiol-containing amino acid that is converted to methionine by methionine synthase with vitamin B_{12} and 5-methyltetrahydrofolate as cofactors. Homocysteine is also converted to cysteine by cystathionine β-synthase, which requires pyridoxine (vitamin B_6) as a cofactor. Congenital causes of hyperhomocysteinemia include homocystinuria (deficiency of cystathionine β-synthase) and inheritance of the thermolabile mutation in the methylene tetrahydrofolate reductase (MTHFR) gene. Homocystinuria is associated with markedly increased levels of homocysteine (> 100 μmol per L) and developmental delay, arterial and venous thromboembolism, eye abnormalities, and premature coronary artery disease. Thermolabile mutations in MTHFR produce much more modest elevations in homocysteine (15 to 30 μmol per L) in only a minority of cases, and generally in association with folate deficiency. Acquired causes of hyperhomocysteinemia include deficiency of vitamin B_{12}, folate and pyridoxine, and renal insufficiency [24].

Hyperhomocysteinemia has been associated with a 20% increase in cardiovascular disease for each 5 μmol per L increase in fasting homocysteine levels [25]. Homozygosity for the MTHFR mutation is associated with a 1.16-fold increased risk of coronary artery disease [26]. This risk appeared to be significantly modified by folate status. Hyperhomocysteinemia is also associated with a two- to threefold higher risk of initial and recurrent VTE [27,28]. However, randomized studies of vitamin supplementation in patients with venous and arterial thrombotic disease did not demonstrate improved clinical outcomes [29–31]. Therefore, the utility of homocysteine lowering therapy is in question. The diagnosis of hyperhomocysteinemia is based on demonstrating elevated levels of homocysteine in a fasting blood sample. Methionine loading prior to sampling can increase the sensitivity of testing.

Elevated Coagulation Factor Levels

Elevated factor VIII (> 95 percentile) has been associated with an increased risk of initial and recurrent VTE [32,33]. Elevated factor VIII levels appear to be inherited, but the responsible genetic alterations have yet to be completely characterized. Factor VIII activity levels are the diagnostic test of choice. This test should be done at least 6 months after an episode of VTE and in the absence of inflammation to avoid spurious elevations. Elevated factor IX and XI antigen levels have been associated with a 2.5- and 2.2-fold increased risk of initial VTE, respectively [34,35].

ACQUIRED PROTHROMBOTIC DISORDERS

Although inherited thrombophilic conditions may lead to thrombosis, the attention paid to their potential presence by physicians and patients alike is often disproportionate, because acquired prothrombotic disorders are much more common and, in many cases, more potent causes of thromboembolism. A list of inherited and acquired prothrombotic disorders is displayed in Table 111.1. In this section, we will review several important acquired thrombotic disorders of relevance to the intensive care.

Cancer

Patients with cancer are at four- to sevenfold increased risk of thromboembolism (venous and arterial) compared with patients without cancer [36,37]. The risks of thromboembolism are influenced by the primary site of cancer, its histology, and stage as well as our treatments for cancer including surgery, chemotherapy, and growth factors such as erythropoietic stimulatory agents. High-risk organ sites include pancreas, brain, and stomach, while lung cancer and colon cancer are associated with intermediate risk and breast cancer and prostate cancer are associated with a lower risk. Adenocarcinoma is associated with a higher risk of thromboembolism than squamous cell carcinoma, and metastatic disease is associated with a higher risk than localized disease. Myeloproliferative disorders, in particular polycythemia vera (PV), are associated with an increased risk of thromboembolism that is mediated at least in part by an increased red cell volume. Therefore, it is essential to control erythrocytosis in patients with PV with phlebotomy (see "Hematologic Conditions" section in the chapter and Chapter 113, "Therapeutic Apheresis: Technical Considerations and Indications in Critical Care"). Surgery increases the risk of thromboembolism by 10-fold, whereas chemotherapy further increases the relative risk of thromboembolism by 50% in cancer patients. Erythropoietic stimulatory agents have been noted to be associated with an increased risk of thrombosis when hemoglobin values exceed 12 g per dL [38].

Unlike congenital thrombophilic states, cancer is associated with both arterial and venous thromboembolism. Thromboembolism can be the first clue to the presence of an occult malignancy. Idiopathic events are 4.8-fold more commonly associated with the presence of occult malignancy than triggered episodes of thromboembolism. The risk of occult malignancy in patients with thromboembolism declines to the background rate in the population over 6 months [39]. Although an randomized clinical trial (RCT) was unable to identify a survival benefit with extensive cancer screening in patients with idiopathic VTE [40], we think it is worthwhile to ensure that patients are up-to-date with preventive healthcare cancer screening (colonoscopy, etc.) and consider computed tomographic scanning to identify occult primaries in patients aged 50 or older presenting with idiopathic VTE.

Cancer patients are also two- to threefold more likely to suffer recurrent VTE and bleeding during therapy [41]. LMWH has been shown to reduce the incidence of recurrent VTE by 50% in patients with cancer, and therefore LMWH rather than oral VKAs should be considered the agent of choice for long-term management of VTE in cancer patients [42].

Heparin-Induced Thrombocytopenia

Thrombocytopenia affects 20% of patients in the ICU [43]. While the true prevalence of heparin-induced thrombocytopenia (HIT) in the ICU is debatable [44], accurate diagnosis and treatment are essential due to the potential thrombotic and hemorrhagic risks associated with the condition.

HIT is an immune-mediated, prothrombotic disorder caused by heparin-dependent, platelet-activating IgG antibodies directed against platelet factor 4 (PF4) that trigger activation of platelets, endothelial cells, and monocytes resulting in consumptive thrombocytopenia and, in 50% of untreated cases,

venous and/or arterial thromboses. Digital/extremity gangrene is a classic finding. Less commonly, skin reactions/necrosis at heparin injection sites or acute systemic reactions (fever, hypotension) occur after heparin administration. Surgical patients (particularly, orthopedic and cardiothoracic) are at high risk for HIT, while medical patients are at intermediate risk and obstetric and pediatric patients are at low risk [45,46]. The clinical probability of HIT can be assessed using the "4 T score," a validated, clinical prediction rule (see Chapter 109 for the elements of the 4 T score) [47]. Management of any patient in whom HIT is being seriously considered requires elimination of exposure to all forms of heparin, and prompt initiation of anticoagulation with a direct thrombin inhibitor (see Chapter 109, "Thrombocytopenia and Platelet Dysfunction"). The clinical diagnosis of HIT should be confirmed with objective laboratory testing, such as the widely available enzyme-linked immunosorbent assay (ELISA assay) for heparin-PF4 antibodies. Patients who develop HIT without thrombosis are typically treated with anticoagulation for 1 to 3 months, whereas patients with thrombosis should be at least 3 to 6 months or longer with warfarin as dictated by the thrombotic event. Without treatment, the mortality of HIT is as high as 20% to 25% with a similar percentage of patients surviving with major complications (e.g., stroke or limb loss). Early diagnosis and treatment has improved mortality and morbidity to 5% to 10% [45,46]. Additional information regarding the pathophysiology and management of HIT is discussed in Chapter 109, "Thrombocytopenia and Platelet Dysfunction."

Major Trauma

Major trauma is an important cause of VTE in the ICU. Fifty-eight percent of trauma patients develop venographic VTE in the absence of thromboprophylaxis [48]. Trauma is a potent stimulus for clot formation because it impacts all three elements of Virchow's triad. Patients are immobilized (stasis) and have extensive vascular and tissue injury (vessel wall damage) leading to tissue factor and collage exposure resulting in activated coagulation (hypercoagulability). Risk factors for VTE in the major trauma patient are listed in Table 111.2 [49,50]. Thromboprophylaxis with enoxaparin (30 mg subcutaneously twice daily), which is much more effective than unfractionated heparin (5,000 units twice daily), can reduce the incidence of VTE by 50% [51]. Mechanical prophylaxis with sequential compression devices and/or graduated compression stocking are a useful adjunctive measure if feasible based on the patient's injuries. Given the high incidence of VTE, intensivists should maintain a high index of suspicion and confirm any clinical findings indicative of thrombosis with objective radiologic testing. Although some have advocated routine radiologic surveillance and prophylactic vena cava filter placement as strategies to reduce VTE in trauma patients, the value of these strategies remains unproven [52,53]. Acute VTE should be managed with conventional anticoagulation. If contraindications to anticoagulation exist, an optional vena cava filter can be placed until the patient is safe for anticoagulation. Once anticoagulation is tolerated, the filter can be removed. As with other patients' triggered episodes of VTE, trauma patients should be treated with warfarin for at least 3 to 6 months, as dictated by their thrombotic event. Catheter-directed or systemic thrombolysis should be reserved for patients with life- or limb-threatening thrombotic events. Catheter or surgical embolectomy is also an option for life-threatening thromboembolism.

TABLE 111.2

RISK FACTORS FOR VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS

Age > 40
Pelvic and or lower extremity fractures with AIS ≥ 3
Head injury with AIS ≥ 3
Mechanical ventilation > 3 d
Major venous injuries
Injuries requiring major surgery
Spinal cord injury
Prolonged immobility
Delayed institution of thromboprophylaxis
Blood transfusions
Femoral venous catheters

AIS, Abbreviated Injury Scale.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS) is an acquired, autoimmune hypercoagulable disorder that is associated with venous and/or arterial thromboembolism, recurrent pregnancy losses, thrombocytopenia, renal insufficiency, vasculitis, and cardiac valvular abnormalities. APS may be primary (not due to any immediately apparent underlying disorder) or secondary, most commonly in association with rheumatologic diseases such as systemic lupus erythematosus (SLE). The diagnostic criteria for APS require the occurrence of one or more objectively documented episodes of thromboembolism or recurrent pregnancy losses in association with positive laboratory testing for a lupus anticoagulant or moderate or high-titer IgG or IgM anticardiolipin antibodies or β_2-glycoprotein I antibodies, performed on at least two occasions 12 or more weeks apart, and at least 12 weeks after the thrombotic insult [54].

The prevalence of elevated anticardiolipin antibodies or lupus anticoagulants in the general population varies from 1% to 5%. In patients with SLE, 15% to 30% have an Lupus Anticoagulants (LA) and 20% to 40% have anticardiolipin antibodies. The mean age of onset of symptoms of APS is 31 years and onset after age 50 years is uncommon [54]. In a mixed population of patients with and without SLE, the incidence of thromboembolism was 2.8% per year [55]. In a cohort of lupus patients, 50% of patients suffered a thromboembolic event over 20 years (2.5% per year) [56]. Patients with a positive lupus anticoagulant or β_2-glycoprotein I antibodies appear to be at higher risk for thromboembolism than patients with anticardiolipin antibodies [57]. In addition, IgG β_2-glycoprotein I antibodies appear to confer a greater risk of thrombosis than IgM antibodies [55,58]. Triple positive patients (i.e., patients positive for lupus anticoagulants, β_2-glycoprotein I antibodies and anticardiolipin antibodies) appear to be very high risk for thromboembolism (recurrent thromboembolism 44% over 10 years) [59].

The most common manifestation of APS that would bring patients to the ICU is venous or arterial thromboembolism. A retrospective review of APS patients noted that 59% had VTE, 28% had arterial thromboembolism, and 13% had both venous and arterial thromboembolism [60]. The diagnosis of APS is made by objectively confirming clinical manifestations (thromboembolism, pregnancy morbidity) and documenting laboratory evidence of antiphospholipid antibodies.

Treatment of VTE of patients with APS is similar to patients with other thrombophilic disorders with several important caveats. APS patients who have an LA often have baseline prolongation of their activated thromboplastin time (aPTT). If the standard therapeutic range is used, these patients' unfractionated heparin may be underdosed. Therefore, patients with a prolonged aPTT at baseline should be treated with an LMWH or have their unfractionated heparin therapy monitored with an anti-Xa heparin activity assay. For chronic antithrombotic

therapy of APS, conventional intensity anticoagulation with a VKA targeting an international normalized ratio (INR) of 2 to 3 is appropriate [57,61,62]. Occasional APS patients will suffer recurrent thromboembolic events despite conventional intensity anticoagulation. In these patients, higher INR targets (INR 3 to 4) or use of alternative anticoagulants (e.g., LMWH, fondaparinux) is appropriate. If a VKA is considered for long-term therapy, it is important to confirm that the patient's antiphospholipid antibody does not prolong the baseline prothrombin time. In occasional APS patients, the INR is not an accurate reflection of anticoagulation and specialized tests such as a chromogenic factor X activity assay must be use for VKA management [63]. Since APS patients are at increased risk for recurrent VTE in the absence of anticoagulation, indefinite anticoagulation is appropriate [64].

For patients with APS and arterial thromboembolism, we also prefer anticoagulation rather than aspirin or antiplatelet agents. Although one study suggested that aspirin and warfarin were equally effective for arterial thromboembolism, participants in this study did not fulfill diagnostic criteria for APS; therefore, we prefer conventional intensity anticoagulation (INR 2 to 3) to aspirin [65].

Catastrophic Antiphospholipid Syndrome

A devastating and life-threatening form of APS that occasionally brings a patient to the ICU is the catastrophic antiphospholipid syndrome (CAPS). CAPS is a rare (< 1% of APS patients present with CAPS) life-threatening manifestation of APS characterized by multiorgan (kidneys, brain, skin, liver, etc.) failure resulting from diffuse microvascular thrombosis. CAPS is often triggered by infections, major surgery, discontinuation of immunosuppression, or anticoagulation. Almost all patients with CAPS require ICU level of care. The mortality associated with CAPS approaches 50%. Common manifestations of CAPS-associated organ involvement are displayed in Table 111.3 [66].

CAPS is thought to result from widespread activation of the endothelium, monocytes, and platelets with tissue factor expression and diffuse activation of the coagulation cascade resulting in widespread microvascular thrombosis and tissue infarction. The diagnostic criteria for CAPS are displayed in Table 111.4. *The differential diagnosis* in patients suspected to have CAPS usually includes severe sepsis, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), disseminated intravascular coagulation (DIC), infectious purpura fulminans, and heparin induced thrombocytopenia thrombosis (HIT/T).

Multimodality therapy is necessary for effective treatment of CAPS. The mainstay of therapy includes anticoagulation (e.g., weight-based unfractionated heparin (UFH) titrated to a therapeutic aPTT) and immunosuppression with corticosteroids (e.g., IV pulse methylprednisolone 1,000 mg per day for 3 to 5 days followed by 1 to 2 mg per kg per day is the most commonly administered dosage). Second-line therapies that are frequently employed in addition to anticoagulation and corticosteroids include intravenous immunoglobulins (IVIG) (total dose of IVIG is 2 g per kg [400 mg per kg for 5 days or 1,000 mg per kg for 2 days]), plasmapheresis, and rituximab (375 mg per m^2 weekly for 4 weeks). Fibrinolytic agents are often used to treat life- or limb-threatening venous or arterial thrombosis. Third-line therapies include cyclophosphamide, prostacyclin (5 ng per kg per minute for 7 days [per case reports]), and defibrotide (100 to 275 mg per kg per day for a minimum of 3 weeks).

TABLE 111.3

CLINICAL MANIFESTATIONS OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Organ system	Manifestations
Blood	Coombs positive hemolytic anemia, autoimmune thrombocytopenia, disseminated intravascular coagulation, bone marrow infarct
Brain	Infarcts, encephalopathy, seizure, transient ischemic attack
Heart	Valvular lesions (Libman-Sacks endocarditis), myocardial infarction, heart failure
Kidney	A 50% increase in serum creatinine, severe systemic hypertension (> 180/100 mm Hg), and/or proteinuria (> 500 mg/24 h)
Lung	Acute respiratory distress syndrome: most common, pulmonary hypertension with normal cardiac output and pulmonary capillary wedge pressure, pulmonary hemorrhage
Skin	Livedo reticularis, skin ulcers, digital ischemia, purpura, skin necrosis
Vasculature	Venous and/or arterial thromboembolism: most common include deep venous thrombosis, pulmonary embolism, extremity artery thromboembolism, portal vein and inferior vena cava thrombosis, retinal artery, and vein thrombosis

TABLE 111.4

DIAGNOSTIC CRITERIA OF CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Diagnostic criteria
1. Evidence of involvement (vascular occlusions) affecting three or more organs, systems, and/or tissues[a]
2. Development of manifestations simultaneously or within 1 week or less
3. Confirmation by histopathology of small vessel occlusion in one organ or tissue[b]
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies)[c]
Definite catastrophic antiphospholipid syndrome
All four criteria are met
Probable catastrophic antiphospholipid syndrome
All four criteria are present but only two organs, systems, or tissues are involved
All four criteria are present but confirmation of laboratory tests 6 wk apart not performed
Criteria 1, 2, and 4 are present
Criteria 1, 3, and 4 are present

[a] Objective evidence of vessel occlusions. A 50% rise in serum creatinine, severe systemic hypertension (> 180/100 mm Hg), and/or significant proteinuria (> 500 mg/24 h) are alternative manifestations of renal involvement.
[b] Thrombosis must be present on histopathology. Vasculitis may be present but is not diagnostic in isolation.
[c] If the patient has not had previous laboratory testing for APS, then laboratory confirmation requires that the presence of antiphospholipid antibodies must be detected on two or more occasions at least 12 wk apart (not necessarily at the time of the event).

Treatment of potential precipitating factors is also extremely important. Such measures include broad-spectrum antibiotics for infections, aggressive hemodynamic resuscitation in case of shock, debridement or amputation for necrotic tissues, mechanical ventilation, renal replacement therapy, tight glycemic control, stomach acid suppression, and control of malignant hypertension in case of renal artery/vein thrombosis. Intravascular instrumentation, especially arterial, should be minimized because of the potential for new clot formation [67].

CAPS mortality rate remains as high as 48% despite all therapies. The clinical manifestations related to poor prognosis and mortality include renal involvement, splenic involvement, pulmonary involvement, adrenal involvement, and SLE diagnosis. CAPS recurrence is unusual. Patients usually have a stable course with continued anticoagulation. One fourth of the survivors will develop further APS-related events, but it is rare to develop recurrent CAPS [67].

Drugs

Certain medications have been associated with an increased risk of thrombosis (Table 111.5). Detection of acute thrombosis in a patient receiving one of these medications typically is a sufficient criterion for discontinuation, and use of such agents in patients with a prior history of thromboembolism must be considered very carefully, weighing the potential benefit against the potential for recurrent thrombosis.

TABLE 111.5

MEDICATIONS COMMONLY ASSOCIATED WITH THROMBOEMBOLISM

Medication	Risk of thromboembolism	Risk factors for thromboembolism	Prevention
Chemotherapy	Two- to sixfold increase	Cancer site—(highest risk—pancreatic, gastric; high risk—lymphoma, gynecologic, bladder, testicular)[a] Prechemotherapy platelet count ≥ 350,000/μL[a] Hemoglobin > 10 g/dL or use of ESA[a] Prechemotherapy WBC > 11,000/μL[a] BMI > 35 kg/m^2[a]	LMWH? In high-risk patients
Estrogen receptor modulators (tamoxifen, raloxifene)	Two- to threefold increase (healthy women breast cancer prophylaxis) 1.5–7 fold increase (adjuvant therapy early breast cancer)	Postmenopausal threefold more likely than premenopausal	N/A
Hormone replacement therapy	Two- to threefold increase	Older age, obesity, thrombophilia, oral > transdermal	N/A
Erythropoietin	1.5-fold	Hemoglobin > 12 g/dL	N/A
Thalidomide, lenalidomide	Alone (1%–3%) With high-dose dexamethasone, combination chemotherapy (10%–20%)	Individual VTE risk factors—obesity, previous VTE, cardiac or renal disease, diabetes, infection immobility, surgery, trauma, erythropoietin use, thrombophilia, recent diagnosis, hyperviscosity[b] Treatment risk factors—high-dose dexamethasone, doxorubicin, or combination chemotherapy[b]	Low risk—(0–1 VTE risk factors, no treatment risk factors)—aspirin[b] High risk—2 or more VTE risk factors or a treatment risk factor)—prophylactic dose LMWH or warfarin (INR 2–3)[b]
Hormonal contraceptives	Three- to fourfold increased risk	Age > 35 y, smoking, obesity, thrombophilia, third > second generation, oral > transdermal, progestin mini-pill < estrogens or combined estrogen/progestins	N/A
Antipsychotics	Twofold	Low potency antipsychotics (e.g., chlorpromazine) > high-potency antipsychotics (e.g., haloperidol); initial 3 mo of therapy, two or more antipsychotics, supratherapeutic serum levels	N/A

[a]Khorana AA, Kuderer NM, Culakova E, et al: Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 111:4902–4907, 2008.

[b]Agnelli G, Gussoni G, Bianchini C, et al; PROTECHT Investigators: Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 10:943–949, 2009.

BMI, body mass index; ESA, erythropoietin stimulating agent; LMWH, low-molecular-weight heparin; INR, international normalized ratio; VIE, venous thromboembolism; WBC, white blood cell.

Hematologic Conditions

Myeloproliferative disorders such as PV and essential thrombocythemia (ET) are associated with an increased risk of thrombotic (arterial and venous) and bleeding complications due to increased blood viscosity associated with erythrocytosis as well as functional abnormalities in leukocytes and platelets and acquired form of von Willebrand disease associated with thrombocytosis. Risk factors for thrombohemorrhagic events include age older than 60 (PV, ET), a previous history of thromboembolism (PV, ET), poorly controlled erythrocytosis (PV), leukocytosis (PV, ET), thrombocytosis (PV, ET), thrombophilia (PV, ET), JAK2 mutation status (PV, ET), and traditional cardiovascular risk factors (hyperlipidemia, smoking, diabetes, and hypertension) (PV, ET). In PV patients, adequate phlebotomy to control erythrocytosis is essential to prevent thrombohemorrhagic complications. Aspirin is useful in PV and ET patients 60 years or older to prevent arterial thromboembolism [68]. In patients who have thrombohemorrhagic events despite these measures, cytoreductive therapy with hydroxyurea, anagrelide, or α-interferon should be prescribed. Anticoagulation is appropriate for patients who suffer VTE [68,69].

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare clonal hematopoietic stem cell disorder that results in the loss of expression of complement regulatory proteins (CD55, CD59) on blood cell membranes. This acquired genetic alteration results in chronic intravascular hemolysis, pancytopenia, and a strong predisposition to venous (more common) and arterial (less common) thrombosis [70,71]. Unusual locations for thrombosis (e.g., hepatic vein thrombosis/Budd–Chiari syndrome, cerebral venous sinus thrombosis, dermal vessel thrombosis) are not uncommon in PNH patients. The diagnosis of PNH can be easily made using flow cytometry to detect the presence/absence of CD55 and CD59 (using antibodies) or glycosylphosphatidylinositol-anchored proteins (GPI-AP) (using fluorescein-labeled aerolysin, a bacterial toxin that binds to all GPI-AP, more sensitive than first technique) on the surface of blood cell membranes. Symptomatic patients with significant hemolysis, fatigue, or end-organ damage or thromboembolism should be treated with eculizumab, a humanized monoclonal antibody against complement protein C5a [71]. For patients with thromboembolism, conventional anticoagulation is appropriate although not always effective in preventing recurrent events. Preliminary data suggest that eculizumab may control the disease process to such an extent that patients with thromboembolism may be able to discontinue anticoagulation [72,73].

DIAGNOSIS APPROACH TO THROMBOPHILIA

Since thrombophilia testing is expensive and has yet to be demonstrated to significantly influence the outcome of patients with thromboembolism [74,75], there should be a strong clinical rationale for considering a thrombophilia evaluation and testing should be focused on patients likely to benefit from the results (Table 111.6). In selected patients, thrombophilia testing may influence the duration of anticoagulation (i.e., in patients with high-risk thrombophilia—AT, PC, or PS deficiency; homozygous FVL; antiphospholipid syndrome; compound heterozygosity for FVL; and the PGM), the management of future pregnancies, provide additional insight into the etiology of a thrombotic event, or improve the adequacy of subsequent VTE prophylaxis efforts during risk periods. These benefits, however, must be weighed against the risks that include increased healthcare insurance costs and unnecessary testing of unaffected family members. Clearly testing should only be performed if it will influence the care of the patient. Therefore, testing should not be performed in patients with idiopathic or recurrent VTE whom you plan to treat indefinitely regardless of the results. Conversely, if the patient has continuing risk factors for bleeding, perhaps the presence of a high-risk thrombophilic state would be sufficient reason to continue anticoagulation despite the presence of these risk factors. In sum, thrombophilia testing should only be done after consideration of its costs and the risks and benefits to the patient [76].

If thrombophilia testing is planned, it should be performed at a time when accurate results can be obtained. Acute thrombosis can result in reductions in AT, PC, and PS activity. Therefore, abnormal results should be interpreted with caution and repeated if possible when the patient is not on anticoagulation. However, if normal results are obtained prior to the initiation of therapy, the patient does not have AT, PC, or PS deficiency. Testing for FVL and PGM may be performed during the acute thrombotic event, as the APC resistance assay and the DNA-based tests are not affected by therapeutic doses of anticoagulation. Fibrinogen assays are generally also insensitive to therapeutic anticoagulation as are antigen assays for factors IX and XI and homocysteine levels. Factor VIII activity should not be measured during an acute episode of thrombosis [76]. Testing for anticardiolipin and β_2-glycoprotein I antibodies can be done during anticoagulation, but lupus anticoagulant testing can be affected by anticoagulation therapy [54]. The timing and recommended tests for prothrombotic conditions are listed in Table 111.7.

It is also important to tailor hypercoagulable testing to the patient's thrombotic process (Table 111.8). FVL and PGM have not been associated with arterial thromboembolism. Therefore, in patients with arterial thrombosis, these tests are not worthwhile ordering, and in patients who are known carriers of FVL or the PGM who suffer an arterial thrombotic event, it is worthwhile looking for another reason for hypercoagulability or for a right-left shunt such as a patent foramen ovale. The link between AT, PC, and, to a somewhat lesser extent, PS and arterial thromboembolism is tenuous and so similar limitations should be considered when testing for these entities. In contrast, cancer, HIT/T, APS, and hyperhomocysteinemia have all been associated with arterial and venous thromboembolism.

TABLE 111.6

CANDIDATE SELECTION FOR LABORATORY TESTING FOR PROTHROMBOTIC CONDITIONS

High yield	Low yield
Young patients (age ≤ 50)	Older patients (age > 50)
Patients with positive family history (first degree relatives)	Patients in situations when artifactual test results may occur (pregnancy, warfarin therapy, etc.)
Patients with idiopathic TE	Patients with cancer
Patients with TE in unusual sites	Patients with strong transient risk factors (major trauma, surgery, etc.)
Patients with recurrent TE	Patients in whom testing will not influence therapy
Patients with warfarin skin necrosis	Patients with arterial TE should not be tested for venous thrombophilic states
Patients planning future pregnancies	

TE, thromboembolism.

TABLE 111.7

LABORATORY TESTING FOR PROTHROMBOTIC CONDITIONS

Condition	Test	Timing	Potential causes of erroneous results
Factor V Leiden	Activated protein C resistance assay	Anytime	Heparin (anti-Xa) level > 1.0 units/mL
	Factor V Leiden DNA-based testing	Anytime	DNA contamination
Prothrombin (factor II) gene mutation	Factor II DNA-based testing	Anytime	DNA contamination
Protein C deficiency	Protein C activity (if abnormal then protein C antigen)	Prior to anticoagulation or after discontinuation	Acute thrombosis, DIC, warfarin, vitamin K deficiency, heparin (anti-Xa) level > 1.0 units/mL, lupus anticoagulant, elevated factor VIII concentrations, liver disease
Protein S deficiency	Protein S activity (if abnormal then total and free protein S antigen)	Prior to anticoagulation or after discontinuation	Acute thrombosis, DIC, warfarin, vitamin K deficiency, estrogen therapy, pregnancy/postpartum, heparin (anti-Xa) level > 1.0 units/mL, lupus anticoagulant, elevated factor VIII concentrations, liver disease
Antithrombin (III) deficiency	Antithrombin activity (if abnormal, antithrombin antigen)	Prior to anticoagulation or after discontinuation	Acute thrombosis, DIC, warfarin, vitamin K deficiency, heparin (anti-Xa) level > 1.0 units/mL, lupus anticoagulant, elevated factor VIII concentrations, liver disease, nephrotic syndrome
Dysfibrinogenemia	Fibrinogen activity (i.e., standard Clauss fibrinogen assay), thrombin time, fibrinogen antigen, reptilase time	Prior to anticoagulation with heparin or direct thrombin inhibitors	Heparin (thrombin time is very sensitive to heparin, fibrinogen less sensitive, reptilase time and fibrinogen antigen insensitive), direct thrombin inhibitors affect thrombin time and fibrinogen activity, myeloma proteins, liver disease
Hyperhomocysteinemia	Homocysteine level	Fasting, with or without methionine loading at anytime	Renal insufficiency, vitamin B_{12} deficiency, folate deficiency
Elevated factor VIII levels	Factor VIII activity	At least 6 mo after thrombotic event in the absence of inflammation	Acute phase response (e.g., infection, inflammation, postsurgery), heparin, direct thrombin inhibitors, DIC
Elevated factor IX levels	Factor IX antigen	At least 6 mo after thrombotic event after discontinuation of warfarin	Acute thrombosis, DIC, warfarin, vitamin K deficiency, liver disease
Elevated factor XI levels	Factor XI antigen	At least 6 mo after thrombotic event	Acute thrombosis, DIC, severe liver disease
Heparin-induced thrombocytopenia	Platelet factor 4 antibody ELISA assay	Anytime	Elevated immune complexes/ immunoglobulin level
	Serotonin release assay	Anytime	
Antiphospholipid syndrome	Activated partial thromboplastin time (low phospholipid reagent) + mixing studies with normal plasma	At diagnosis of thrombotic event and at least 12 wk later	Heparin, direct thrombin inhibitors
	Dilute Russell Viper venom time with confirm procedure	At diagnosis of thrombotic event and at least 12 wk later	Heparin (anti-Xa) level > 1.0 units/mL, direct thrombin inhibitor, fondaparinux, warfarin (?), factor X, V, and II inhibitors
	Platelet neutralization procedure	At diagnosis of thrombotic event and at least 12 wk later	Heparin, factor V deficiency/inhibitors
	Anticardiolipin antibody ELISA	At diagnosis of thrombotic event and at least 12 wk later	Rheumatoid factor, Syphilis and HIV can result in positive test and must be ruled out
	β_2-Glycoprotein I antibody ELISA	At diagnosis of thrombotic event and at least 12 wk later	Rheumatoid factor can produce false-positive results

DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; ELISA, enzyme-linked immunosorbent assay.

TABLE 111.8

SELECTED META-ANALYSES AND PROSPECTIVE STUDIES IN THROMBOPHILIC DISORDERS

Thrombophilic disorder	Characteristic	Study methodology	Reference
Factor V Leiden (FVL)	FVL heterozygosity and homozygosity are associated with a 5- and 10-fold increased risk of VTE	Meta-analysis of eight case–control studies including 2,310 cases and 3,204 controls	Emmerich J et al. [8]
	FVL is not a risk factor for myocardial infarction (OR, 1.24 [95% CI, 0.91–1.69] and RR, 0.83 [0.58–1.20]) or stroke (OR, 0.92 [95% CI, 0.56–1.53] and RR, 0.68 (0.45–1.04)	Meta-analysis of three case-control studies and three prospective observational studies	Juul K et al. [9]
	FVL heterozygosity and homozygosity increase the risk of recurrent thrombosis by 1.56-fold (95% CI, 1.14–2.12) and 2.65-fold (95% CI, 1.18–5.97), respectively; FVL is not	Meta-analysis of 46 studies	Segal J et al. [10]
Prothrombin gene mutation	Heterozygous factor II mutation associated with a 3.8-fold increased risk of VTE	Meta-analysis of 8 case–control studies including 2,310 cases and 3,204 controls	Emmerich J et al. [8]
	Prothrombin gene mutation is not associated with myocardial infarction (RR, 0.8 [0.4–1.6]) or stroke (RR, 1.1 [0.5–2.4])	Prospective cohort study of 14,916 U.S. men	Ridker P et al. [13]
	The prothrombin gene mutation is not associated with recurrent VTE (OR, 1.45; 95% CI, 0.96–2.2).	Meta-analysis of 46 studies	Segal J et al. [10]
Compound heterozygotes for FVL and the prothrombin gene mutation	Compound heterozygotes for FVL and the factor II mutation are at 20-fold (95% CI, 11.1–36.1) increased risk for VTE	Meta-analysis of eight case–control studies including 2,310 cases and 3,204 controls	Emmerich J et al. [8]
	The OR for recurrent VTE in compound heterozygotes for FVL and the factor II mutation is 4.81 (95% CI, 0.50–46.3)	Meta-analysis of 46 studies	Segal J et al. [10]
Hyperhomocysteinemia	Homocysteine lowering vitamin supplementation does not reduce the incidence of recurrent VTE	Two prospective, randomized, controlled trials	Ray JG et al. [29] and den Heijer M et al. [30]
	Homocysteine lowering vitamin supplementation does not reduce the incidence of cardiovascular disease in post-MI patients	Prospective, randomized, controlled trial of 5,522 patients	Lonn E et al. [31]
Antiphospholipid syndrome	High intensity vitamin K antagonist therapy (INR, 3–4) is not superior to conventional intensity therapy (INR, 2–3) for treatment of APS patients with previous VTE9	Two prospective, randomized, controlled trials	Crowther M et al. [61] and Finazzi G et al. [62]

CI, confidence interval; INR, international normalized ratio; MI, myocardial infarction; OR, odds ratio; RR, relative risk; VTE, venous thromboembolism.

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CHAPTER 112 ■ ANEMIA IN THE CRITICAL CARE SETTING

MARC S. ZUMBERG, MARC J. KAHN AND ALICE D. MA

GENERAL PRINCIPLES

Anemia is common in the critical care setting. Recent studies have shown that 29% to 62% of patients have anemia at the time of admission to critical care units and 20% to 30% have moderate or severe anemia (hemoglobin < 9 g per dL) [1–5]. Anemia will develop in nearly all patients at some point during the course of a prolonged intensive care unit (ICU) stay, and as a result, the majority of patients admitted more than 7 days receive a red blood cell (RBC) transfusion [1–5].

Certain anemias may be encountered more frequently in patients who are admitted to critical care units than in other settings, including anemias arising from iatrogenic sources (e.g., mechanical hemolysis caused by ventricular assist devices or intra-aortic balloon pumps); those producing hemodynamic or systemic compromise that leads to a requirement for critical care (e.g., massive blood loss due to trauma, gastrointestinal lesions, or surgical invasion; thrombotic microangiopathies); and those arising in the context of prolonged critical illness (e.g., anemia of chronic disease/inflammation [ACD]). Losses from an enhanced frequency of phlebotomy for diagnostic testing in the critical care unit may contribute to the development or maintenance of anemia and have been estimated to account for 1 to 2 units lost during a typical hospital stay [5,6].

This chapter provides an overview of the evaluation and laboratory workup of anemia, with a focus on diagnoses that provoke the most clinical concern, are important to recognize quickly, and are the most likely to be encountered in the critical care setting. Accordingly, the hemolytic anemias, including the microangiopathic hemolytic anemias, autoimmune hemolytic anemia (AIHA), and sickle cell syndromes, will be covered in the most detail (Table 112.1). The ACD often develops in patients in the ICU and will also be a focus of this chapter. Anemia due to massive blood loss including trauma and gastrointestinal bleeding is essential to recognize, obtain proper consultation for, and treat appropriately, but the diagnosis is usually self-evident.

Initial Evaluation

The etiologies of anemia in the critical care setting are diverse, but the evaluation of anemia in a critical care patient initially should be approached in a manner similar to the noncritical care setting.

The patient's volume status should be considered first, as an increase in the plasma volume may lead to a decrease in the measured hemoglobin or hematocrit that does not represent a decrease in the red cell mass or oxygen carrying capacity. This situation is known as dilutional or spurious anemia and is particularly common in ICU patients requiring fluid resuscitation [5]. Dilutional anemia does not require treatment.

To better come up with a differential diagnosis of the anemia, it should be determined whether the anemia predated the patient's critical illness, developed in conjunction with the critical illness, or developed during the ICU stay (Table 112.2).

TABLE 112.1

CLASSIFICATION OF THE HEMOLYTIC ANEMIAS: CONGENITAL VERSUS ACQUIRED

Congenital hemolytic anemias
Defects in the erythrocyte membrane
- e.g., hereditary spherocytosis

Deficiencies in erythrocyte metabolic enzymes
- ex. pyruvate kinase deficiency
- ex. glucose-6-phosphate dehydrogenase deficiency

Defects in globin structure and synthesis
- ex. sickle cell disease
- ex. thalassemia

Acquired hemolytic anemias
Autoimmune hemolytic anemias
- ex. warm autoimmune hemolytic anemia
- ex. cold agglutinin disease
- ex. paroxysmal cold hemoglobinuria
- ex. drug-induced hemolytic anemia

Microangiopathic hemolytic anemia
- ex. thrombotic thrombocytopenic purpura
- ex. hemolytic uremic syndrome
- ex. disseminated intravascular coagulation

Hemolytic transfusion reaction
Paroxysmal nocturnal hemoglobinuria
Infectious agents
- ex. malaria

Chemicals, drugs, and physical agents
- ex. arsenic

Advanced liver disease

Laboratory Studies

Anemias can be classified by the size of the RBCs as reflected by the mean corpuscular volume (MCV): microcytic (MCV, < 80 fL), normocytic (80 to 100 fL), and macrocytic (> 100 fL). A finite number of diagnoses constitute each of these categories, allowing the practitioner to narrow the differential diagnosis (Table 112.3). One should take caution to review the MCV prior to the transfusion of RBCs, as donor RBCs may increase or decrease the MCV depending on the pretransfusion value.

TABLE 112.2

SAMPLE DIFFERENTIAL DIAGNOSIS OF ANEMIA BASED ON THE TIME COURSE OF ANEMIA IN RELATION TO THE CRITICAL ILLNESS

Anemia predating the critical illness
- Primary bone marrow disorders
- Vitamin deficiencies
- Hemoglobinopathies
- Congenital anemias

Anemia developing in conjunction with the critical illness
- Anemia of chronic disease/inflammation
- Hemolytic anemias
- Thrombotic thrombocytopenic purpura

Anemia developing during the course of the intensive care unit stay
- Gastrointestinal bleeding
- Frequent phlebotomies
- Drug-induced hemolytic anemia
- Anemia of chronic disease/inflammation

TABLE 112.3

DIFFERENTIAL DIAGNOSIS OF SELECTED ANEMIAS BASED ON RED CELL MEAN CORPUSCULAR VOLUME (MCV)

Microcytic (MCV ≤ 80 fl)
- Fe deficiency
- α-Thalassemia
- β-Thalassemia
- Anemia of chronic disease/inflammation
- Lead poisoning
- Sideroblastic anemia

Normocytic (MCV 80–100 fl)
- Acute blood loss
- Primary bone marrow disorders
- Anemia of chronic disease/inflammation
- Splenomegaly
- Hemolytic anemia with low or normal reticulocyte count
- Endocrine disorders

Macrocytic (MCV > 100 fl)
- Megaloblastic anemia
  - B_{12} deficiency
  - Folic acid deficiency
  - Drug induced
- Hypothyroidism
- Liver disease
- Hemolytic anemia with reticulocytosis
- Myelodysplastic syndrome

Several additional tests may be helpful in the evaluation of anemia. The reticulocyte count, which is a measure of the bone marrow's ability to produce new RBCs, should be the initial test performed. The reticulocyte count is typically elevated in hemolytic anemias, gastrointestinal bleeding, or after supplementation of a missing nutrient such as iron or vitamin B_{12}. The reticulocyte count is typically low in primary bone marrow failure disorders, nutritional deficiencies, the anemia of chronic disease/inflammation, and any condition leading to the underproduction of or resistance to erythropoietin (e.g., renal disease). If a hemolytic anemia is suspected (i.e., due to consistently hemolyzed blood specimens, characteristic findings on physical examination [see later], or refractoriness to erythrocyte transfusion), measurement of total and unfractionated bilirubin (elevated), lactate dehydrogenase (LDH) (elevated), and haptoglobin (decreased) may be useful, although the results are not specific to hemolysis and may be similar in patients with advanced liver disease.

The blood smear itself may help to narrow the diagnosis and quickly identify anemias due to causes that require expeditious, specialized management (e.g., thrombotic microangiopathies). Examples of erythrocyte abnormalities include schistocytes (Fig. 112.1), sickle cells (Fig. 112.2), bite cells (Fig. 112.3), or spherocytes (Fig. 112.4) and identification of these aberrant forms is critical in making the correct diagnosis (Table 112.4).

Further laboratory testing should be guided by the results of the MCV, reticulocyte count, review of the blood smear, and any clinical suspicion of likely diagnoses (Table 112.5).

Therapeutic Red Cell Transfusion

Clinicians caring for patients in critical care settings are often confronted with the decision to transfuse RBCs even before results of laboratory testing or other evaluation has elucidated

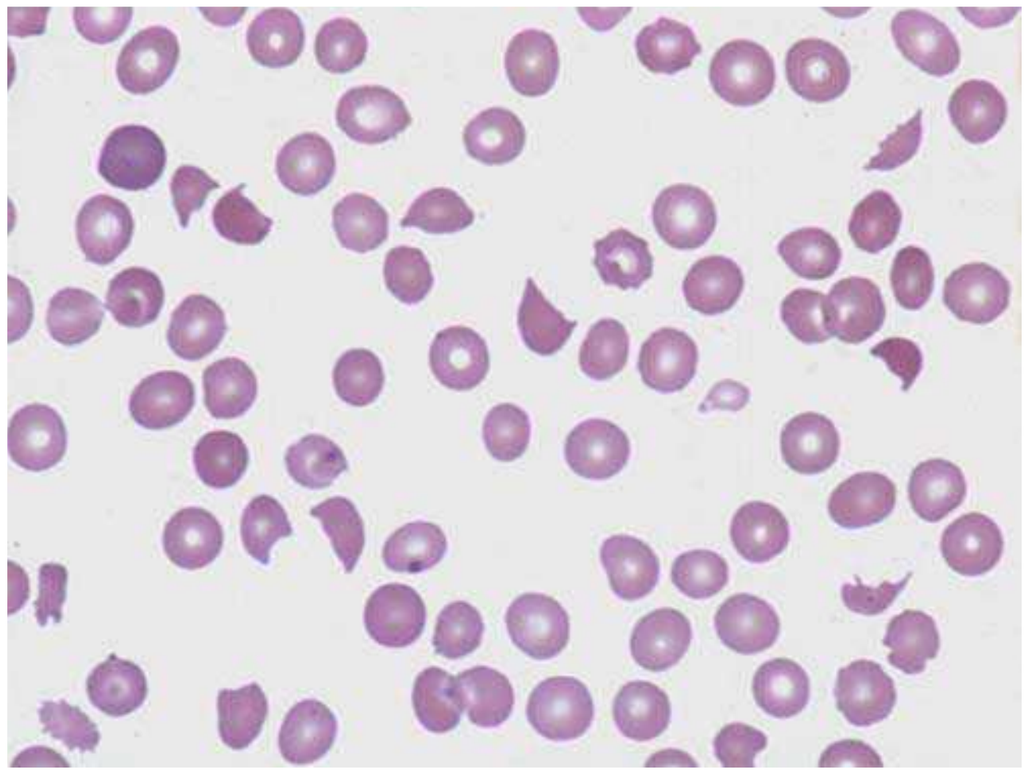

FIGURE 112.1. Peripheral smear from a patient with disseminated intravascular coagulation shows characteristic "helmet: cells. [Reused with permission from Maslak P. ASH Image Bank 2008;2008:8-00102.]

the cause of the anemia. Erythrocyte transfusion in this setting may be guided by hemodynamic considerations, rather than a finite transfusion trigger [7]. Because of the (albeit low) risk of transmission of infectious pathogens and the potential for transfusion reactions and immunomodulation, and in light of increasing evidence from randomized trials that anemia is well tolerated in individuals without cardiopulmonary compromise, more restrictive transfusion policies are becoming more common [8–12]. Principles of transfusion are discussed in greater detail in Chapter 114.

Use of Erythropoiesis-Stimulating Agents

In multiple randomized clinical studies, use of erythropoiesis-stimulating agents (ESAs) in critically ill patients as compared

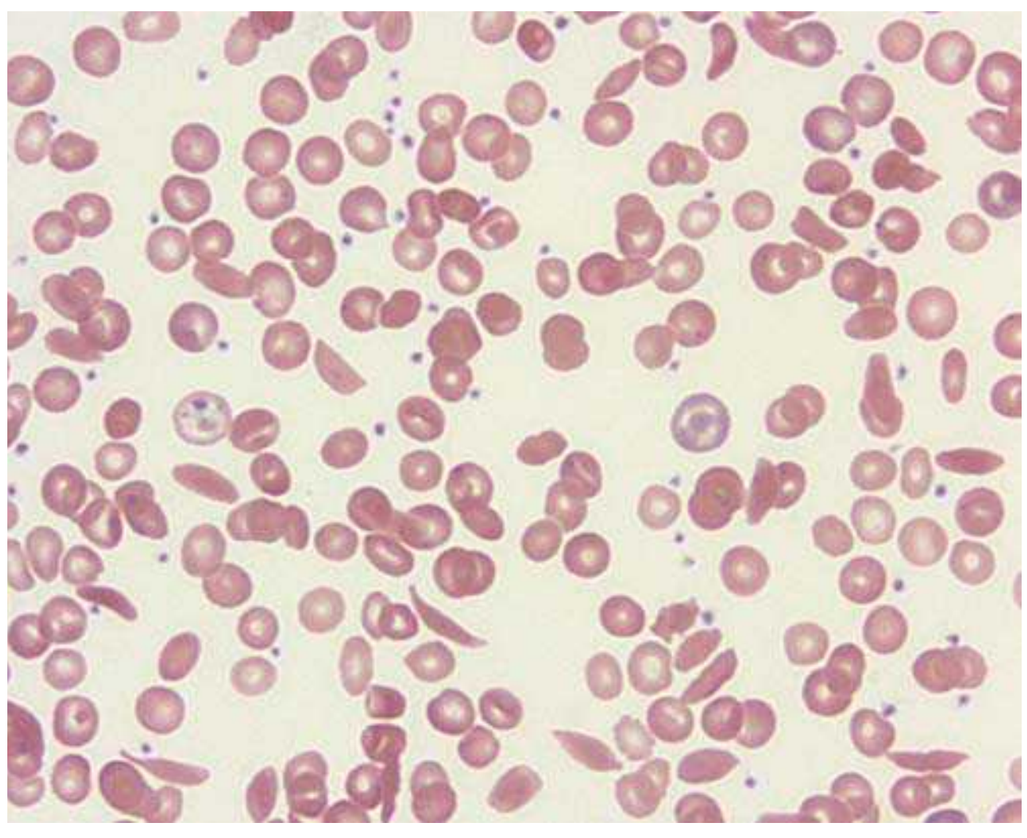

FIGURE 112.2. Peripheral smear from a patient with sickle cell disease illustrates the spectrum of RBC findings in this disorder including sickle cells, polychromatophilic RBCs, target cells, and Howell-Jolly bodies. [Reused with permission from Lazarchick J. ASH Image Bank 2009;2009:9-00044.]

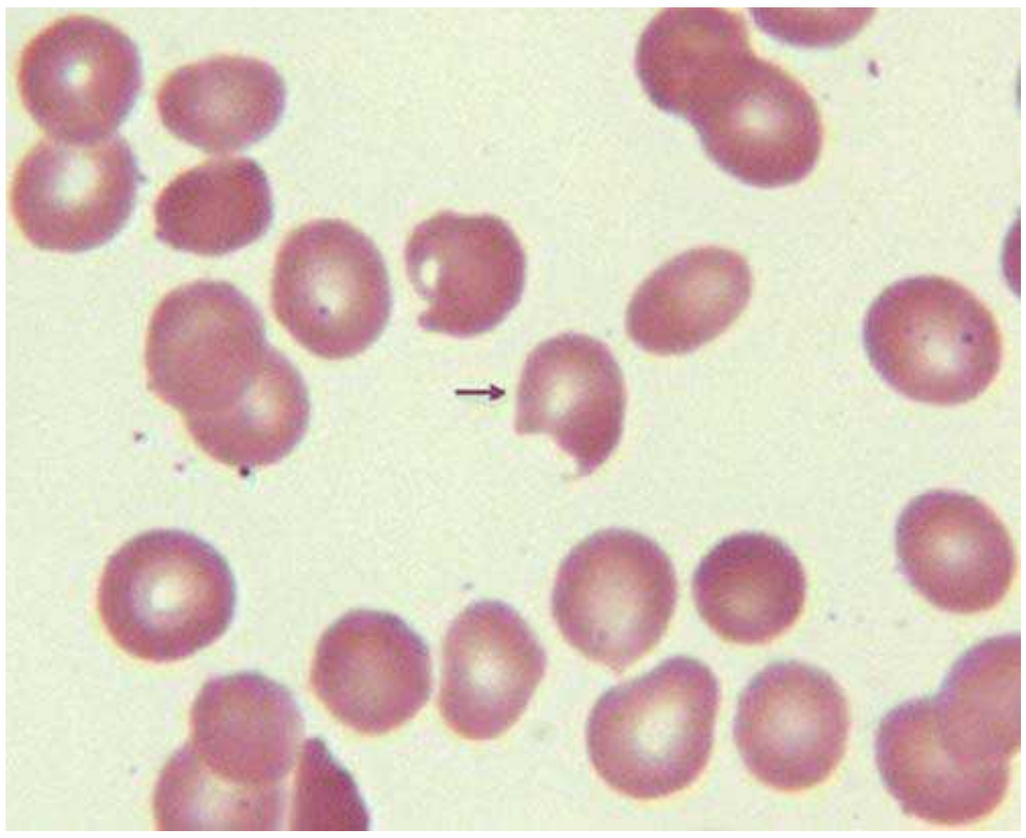

FIGURE 112.3. The RBC deformity (*arrow*) shown in this image is referred to as a "bite" cell. [Reused with permission from Lazarchick J. ASH Image Bank 2008;2008:8-00151.]

with placebo or no intervention had no statistically significant effect on overall mortality, length of hospital stay, ICU stay, or duration of mechanical ventilation [13,14]. A recent meta-analysis, however, has shown that use of ESAs reduced the odds of a patient receiving at least one transfusion and modestly decreased the mean number of units of blood transfused by 0.41 units [13]. The optimal dosing and schedule of erythropoietin remains to be determined [13,15–17], and the need for concomitant supplemental intravenous iron, which may be considered when the serum ferritin drops below 100 to 200 ng per mL or iron saturation drops below 20% [2,15], still is debated. In a recent U.S. multicenter, retrospective, observational study of ESA utilization in anemic critically ill patients admitted to the ICU, practice patterns were highly variable [18]. Thus, at the present time, there remains insufficient evidence to recommend the routine use of ESAs in critically ill anemic patients [13].

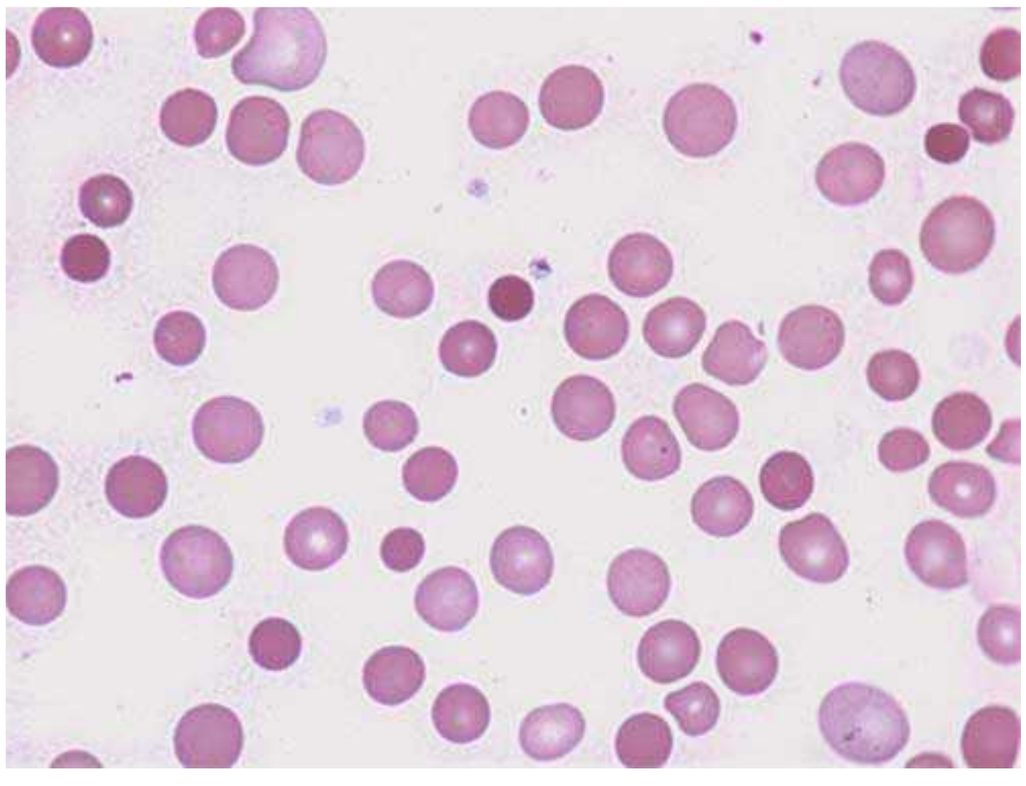

FIGURE 112.4. Spherocytes lack central pallor and may appear smaller than typical red cells. [Reused with permission from Maslak P. ASH Image Bank 2008;2008:8-00103.]

TABLE 112.4

SELECTED BLOOD SMEAR MORPHOLOGIC FINDINGS USEFUL IN THE EVALUATION OF HEMOLYTIC ANEMIA

RBC findings	Associated conditions
Nucleated red blood cells	Hemolytic anemia, postsplenectomy, infiltrative bone marrow process, "revved-up" bone marrow
Schistocytes	Microangiopathic hemolytic anemia including TTP, HUS, HELLP syndrome, DIC, heart valve hemolysis, malignant hypertension
Sickle cells	Sickle cell disease, sickle-thalassemic syndromes
Target cells	Thalassemia, liver disease, hemoglobin C
Spherocytes	Hereditary spherocytosis, warm autoimmune hemolytic anemia
Bite cells	G6PD deficiency
Tear drop cells	Myelofibrosis, infiltrative bone marrow process
RBC agglutination	Cold agglutinin disease
Rouleaux formation	Multiple myeloma, Waldenstrom's macroglobulinemia

DIC, disseminated intravascular coagulation; G6PD, glucose 6 phosphate dehydrogenase; HELLP syndrome, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

Hematology Consultation

If the etiology of the anemia is not apparent despite the above evaluation or if treatment options remain uncertain, hematology consultation should be initiated. A bone marrow aspirate and biopsy may be useful if the diagnosis remains in question or if a primary bone marrow disorder is suspected due to unexplained abnormalities (morphologic or quantitative) in other blood cell lineages.

HEMOLYTIC ANEMIAS

The hemolytic anemias are characterized by a decreased red cell life span. The physiologic sequelae of these disorders, in addition to the ability of the hemolytic process to cause a decrease in hemoglobin and oxygen carrying capacity in a short period of time, may lead to a requirement for critical care. The patient with hemolysis may be very or only minimally symptomatic, depending on the rate of red cell destruction and the degree of compensation by the bone marrow, which produces young red cells (reticulocytes) in response to the decreased hemoglobin.

Overview of Laboratory Features

Pathologic features of hemolysis differ greatly depending on whether the red cell destruction is primarily intravascular or extravascular. Biochemical evidence for intravascular hemolysis includes elevated levels of LDH and unconjugated bilirubin and decreased levels of haptoglobin, which is cleared from the

TABLE 112.5

SUGGESTED INITIAL SAMPLE LABORATORY EVALUATION BASED ON THE MCV AND RETICULOCYTE COUNT

Laboratory finding	Suspected diagnoses	Diagnostic studies[a]
Decreased MCV/low reticulocyte count	Iron deficiency Thalassemia trait Sideroblastic anemia	Iron studies Hemoglobinopathy evaluation Bone marrow aspirate/biopsy
Decreased MCV/high reticulocyte count	Thalassemia	Hemoglobinopathy evaluation
Normal MCV/low reticulocyte count	Organ dysfunction Anemia of chronic disease Early iron deficiency HIV Multiple myeloma Other bone marrow disorders	Electrolytes, LFTs, TSH, EPO Iron studies, electrolytes, LFTs Iron studies HIV studies Serum protein electrophoresis Bone marrow aspirate/biopsy
Normal MCV/high reticulocyte count	GI bleed Hemolytic anemia	Guaiac stool, endoscopy LDH, bilirubin, haptoglobin, Coombs test
High MCV/low reticulocyte count	Vitamin deficiencies Hypothyroidism Advanced liver disease Bone marrow disorders	Vitamin B_{12}, folic acid TSH LFTs Bone marrow aspirate/biopsy
High MCV/high reticulocyte count	Hemolytic anemia	LDH, bilirubin, haptoglobin, Coombs test

[a]Diagnostic studies may be ordered in succession until diagnostic result is reached.
EPO, erythropoietin; GI, gastrointestinal; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; LFTs, liver function tests; MCV, mean corpuscular volume; TSH, thyroid stimulating hormone.

circulation after binding free hemoglobin. Hemoglobinuria results when free hemoglobin is filtered through the glomerulus and is released into the urine, imparting a reddish color. Some hemoglobin in the urine is taken up by tubular cells and is converted to hemosiderin. This can be detected by checking for intracellular iron in the urine by staining the urine with Prussian blue stain. Extravascular hemolysis may be evidenced by only a declining hemoglobin level, although cases of brisk destruction of red cells may show elevations in LDH and unconjugated bilirubin.

Increased red cell production is evidenced by an increase in the number of circulating reticulocytes, which are young red cells whose large size typically results in an elevated red cell MCV and red cell distribution width. Circulating nucleated red blood cells (NRBCs) may be seen in cases of brisk hemolysis. Morphologic evidence of red cell destruction may be evident on the blood smear (see following sections and Figs. 112.1 to 112.4).

Immune-Mediated Hemolysis

The pathophysiology of immune-mediated hemolysis involves antibodies binding to red cells, with or without the activation of complement, leading to red cell destruction. If the antibody on the red cell surface is immunoglobulin G (IgG), then red cell destruction is mediated via Fc receptors on macrophages within the reticuloendothelial (RE) system. Complete or partial phagocytosis occurs causing the red cells to take a spherocytic shape as opposed to the normal, more pliable, biconcave disc shape.

Antibodies which lead to hemolysis can be divided into two categories: warm and cold, referring to the temperature at which the antibody optimally reacts with the red cell. Warm antibodies react with red cells best at temperatures 37°C and typically do not agglutinate red cells [19]. Cold antibodies typically react best at temperatures less than 32°C, with maximal reactivity at 4°C and lead to red cell agglutination [20]. The hallmark of AIHA is a positive direct Coombs test, which will detect the presence of either IgG or C3 bound to red cells (Table 112.6).

Warm Autoimmune Hemolytic Anemia

In warm autoimmune hemolytic anemia (WAIHA), IgG antibodies are directed against red cell surface membrane antigens [19]. Most commonly, these antibodies are directed against members of the Rh blood group, but the specificity of the pathogenic IgG antibodies is not always identified. The IgG antibodies coat the red cells and may or may not fix complement (C3). IgG-coated red cell membrane fragments are engulfed by macrophages in the RE system (usually the spleen) [19,21]. As the red cell loses surface area, it loses the ability to retain its biconcave disc shape. Since the shape with the smallest surface area-to-volume ratio is a sphere, the red cell becomes progressively more spherocytic with each pass through the splenic circulation [19].

WAIHA can manifest as a primary disorder, or alternatively, it can be secondary to an underlying disorder, such as collagen vascular disease (e.g., lupus) or a lymphoproliferative disorder (e.g., lymphoma). Approximately 30% of patients with chronic lymphocytic leukemia have a positive Coombs test, although a much lower proportion develops hemolysis [22]. AIHA may be associated with immune thrombocytopenia, a condition called Evans syndrome. AIHA can also be provoked by infection or can be induced by various drugs. Causes of WAIHA are listed in Table 112.7.

TABLE 112.6

INTERPRETATION OF THE COOMBS TEST AND DIFFERENTIAL DIAGNOSIS

	IgG positive	IgG negative
C3 positive	WAIHA Drug-induced hemolysis	Drug-induced hemolysis Cold agglutinin disease PCH
C3 negative	WAIHA	WAIHA (rare)

Notes: In performing this test, red cells from the patient are washed to remove nonspecific proteins and antibodies. Next, antibodies to human IgG, human C3, or both are added to the cells. If the patient's red cells have either IgG or C3 attached to them, the red cells will agglutinate, indicating a positive test. The specificity of the antibody can be tested by testing the patient's serum against panels of red cells that express different subsets of red cell antigens.
IgG, immunoglobulin G; PCH, paroxysmal cold hemoglobinuria; WAIHA, warm autoimmune hemolytic anemia.

TABLE 112.7

CAUSES OF IMMUNE HEMOLYTIC ANEMIAS

- Warm autoimmune hemolytic Anemia
  - Idiopathic
  - Lymphoproliferative disease
  - Autoimmune disease
  - Drugs
  - Infections
  - Solid tumors
- Cold agglutinin disease
  - Idiopathic
  - Lymphoproliferative disease
  - Infections

Clinical Features. Almost all patients present with worsening and often debilitating fatigue. Older patients, and those with rapid hemolysis and ensuing severe anemia, may present with evidence of organ compromise such as dyspnea, angina, or syncope and can suffer myocardial ischemia, hypotension, and/or renal failure. Physical findings can include pallor, jaundice, and splenomegaly. Laboratory findings include an increased reticulocyte count, increased bilirubin (total and indirect), and increased LDH. The direct Coombs test should be positive (Table 112.6), and typically spherocytes, microspherocytes, NRBCs, and/or anisocytosis are seen on the blood smear.

Transfusion in Patients with Warm Autoimmune Hemolytic Anemia. If the patient has heart failure, angina, shock, or evidence of hypoperfusion to vital organs, or if compensatory erythrocytosis is absent or inadequate due to an underlying illness that suppresses the bone marrow, such as leukemia, prior chemotherapy, or renal failure, then red cell transfusion should be performed [19]. The anti-erythrocyte autoantibody itself also occasionally can be directed against red cell precursors in the marrow, leading to an inappropriately low reticulocyte count [19,23]. Any transfusion in patients with WAIHA needs to be coordinated closely with the blood bank or transfusion service. The offending antibody will frequently interfere with performing a crossmatch to identify compatible blood for transfusion. It is critical to obtain a thorough transfusion and pregnancy history to determine the likelihood of an underlying alloantibody which may be masked by the autoantibody; testing a red cell eluate may be helpful in this regard. Crossmatching can be done using low ionic strength solution (LISS) which

will minimize nonspecific interactions, allowing the stronger alloantibody interactions to appear. If time allows, phenotyping can be performed to identify any antigens on the patient's red cells that may be likely to engender an immune reaction when exposed to transfused blood; such a maneuver may help to minimize the risk of a delayed hemolytic transfusion reaction (DHTR). If crossmatched units are not available, phenotypically matched red cells are preferred. If not available, due to time constraints or the patient's condition, then ABO and Rh type-specific, noncrossmatched, or "least incompatible" units should be used. Each unit should be transfused slowly, while the patient's clinical status is closely assessed for evidence of worsening hemolysis. The blood bank may require that samples of the patient's blood be drawn soon after the transfusion begins to record any evidence of hemolysis. This is termed an in vivo crossmatch.

Treatment. After hemostatic instability has been addressed through transfusion of RBCs, the initial treatment of WAIHA consists of immunosuppression which, if successful, may attenuate antibody production and allow the patient's RBCs to survive normally in the circulation. First-line therapy consists of glucocorticosteroids, either intravenously such as methylprednisolone or oral prednisone, typically at 1 to 2 mg per kg daily [19]. Intravenous immunoglobulin (IVIG) has also been used but is less effective than in immune thrombocytopenic purpura (ITP) [19,24]. If steroids are ineffective, or if relapse occurs, then alternative immunosuppression should be considered. Agents which have been reported to be useful in WAIHA include rituximab, cyclophosphamide, mycophenolate mofetil, and azathioprine [19,25–27]. Splenectomy should also be considered as a reasonable second-line treatment option in eligible patients [19]. As with all hemolytic anemias, the administration of folic acid 1 to 5 mg per day, at least as long as hemolysis is ongoing, is recommended. The reticulocyte count and complete blood cell count (CBC) should be followed closely to monitor the effectiveness of therapy. The amount of blood drawn may be minimized by using pediatric tubes or "bullet" tubes, if available.

Cold Agglutinin Disease

In cold agglutinin disease (CAD), immunoglobulin M (IgM) antibodies target red cell surface antigens, typically with specificity to either "I" or "i." These IgM antibodies optimally bind to red cells at "cold" temperatures (typically $< 32^{\circ}C$ and most strongly at $4^{\circ}C$) [20], and, given their ability to bind more than one RBC simultaneously, lead to the agglutination and clumping of RBCs in the distal microvasculature. IgM antierythrocyte antibodies fix complement to the red cell, leading to either intravascular or extravascular hemolysis. CAD may be primary or secondary due to disorders such as lymphoproliferation or infection [28,29].

Clinical Features. In most patients, CAD is a chronic condition characterized by mild to moderate hemolysis and episodic cyanosis and ischemia of the ears, tip of the nose, and digits [29]. When episodic, cold-induced hemolytic episodes occur, intravascular hemolysis may be associated with shock, rigors, back pain, and renal failure.

Laboratory Evaluation. Cold-agglutinin titers can be measured. On Coombs testing, complement (C3) is typically positive while IgG is negative, reflecting the underlying IgM autoantibody which more efficiently fixes complement (Table 112.6). The thermal amplitude of the autoantibody, not the antibody titer, however, best determines the severity of clinical symptoms. If binding occurs only at $4^{\circ}C$ to $30^{\circ}C$, it is less clinically important than if significant binding occurs at temperatures more than $34^{\circ}C$, approximating more physiologic conditions. In fact, many normal individuals will have cold agglutinins detected at $4^{\circ}C$ but have no clinical symptoms.

Treatment. In patients with chronic, mild CAD, the mainstay of treatment is avoidance of cold temperatures. Corticosteroids and splenectomy are typically ineffective in CAD as compared with WAIHA. Other agents, such as chlorambucil, cyclophosphamide, and rituximab, have been used successfully [20,30]. In patients who present with impending or actual end-organ damage such as myocardial ischemia or stroke, plasmapheresis may be effective because IgM remains primarily intravascular and can be efficiently removed. Plasmapheresis may need to be performed preoperatively in surgeries requiring cardiopulmonary bypass or cardioplegia [20,31]. In all patients, care must be taken to keep the extracorporeal tubing warm and to warm intravenous fluids and blood products, or hemolysis may worsen. Folic acid repletion is recommended in all patients.

Paroxysmal Cold Hemoglobinuria

IgG is the pathogenic antibody in this rare condition. Similar to IgM antibodies in CAD, the IgG antibody in paroxysmal cold hemoglobinuria (PCH) binds to red cells only at cold temperatures where it fixes complement. Unlike the antibody in CAD, however, it is activated at warmer temperatures and does not agglutinate red cells. This antibody is called the Donath-Landsteiner antibody and is directed against the "P" red cell antigen [20]. Red cell destruction occurs primarily via activation of the complement cascade and leads to subsequent intravascular hemolysis. In the past, PCH was primarily a disease associated with tertiary syphilis and, therefore, has become much less common in the penicillin era. Currently, PCH is primarily a pediatric disorder (often following a viral infection), only rarely affecting adults. Patients suffer episodic, cold-induced hemolysis. There is no cold-induced digital ischemia.

The diagnosis is made by detection of the Donath-Landsteiner antibody. The Coombs test is typically negative for IgG and positive for C3 (Table 112.6). The blood bank should be alerted to the possibility of this diagnosis, as special considerations are required for detection. Serum is collected from the patient and kept at $37^{\circ}C$. Patient serum and normal red cells are next chilled to $4^{\circ}C$ then warmed to $37^{\circ}C$. The presence of lysis is revealed by detection of free hemoglobin in the sample. Controls must be performed where red cells and serum are incubated at $37^{\circ}C$ and in a separate test tube at $4^{\circ}C$. In both of these scenarios, there should be no lysis detected [32], as a positive test requires the extremes of temperature.

Drug-Induced Hemolytic Anemias

More than 130 drugs have been reported to cause immune-mediated hemolytic anemia [33]. Drugs can induce hemolytic anemia by three general mechanisms: the innocent bystander mechanism, hapten mechanism, and a true autoimmune mechanism [34,35]. These are described in Table 112.8. It should be noted that many drugs may lead to a positive direct Coombs test in the absence of overt hemolysis. Thus, a positive direct Coombs test should not be inferred to represent hemolysis unless there is worsening anemia in conjunction with consistent laboratory evaluation.

Other drugs may cause hemolysis by alternative mechanisms. Oxidant agents such as dapsone and other sulfa drugs may cause hemolysis in a dose-dependent fashion, especially in individuals with glucose 6-phosphate dehydrogenase (G6PD) deficiency who are impaired in their ability to detoxify the oxidant damage to hemoglobin (see "Glucose 6-Phosphate Dehydrogenase Deficiency" section later in the chapter). Ribavirin,

TABLE 112.8

MECHANISMS OF DRUG-INDUCED HEMOLYSIS

Mechanism	Pathophysiology	Examples
Innocent bystander mechanism	Antibodies develop against the drug. The drug and antibody bind together to form immune complexes, which deposit on the surface of the red cell, where they are recognized by the RE system. The drug must be present in order for hemolysis to occur	Quinine Quinidine Isoniazid
Hapten mechanism	Drug binds to the red cell surface, and antibodies form which are directed against the complex of RBC/drug	Penicillins Cephalosporins, especially Cefotetan
True autoimmune mechanism	Certain drugs appear to induce formation of antibodies directed against red cell surface components, independent of any binding to the RBC surface. Once the process has been initiated, antibody production can continue, even in the absence of drug	Alpha methyldopa Levodopa Procainamide Fludarabine

RBC, red blood cell; RE, reticuloendothelial.

used to treat hepatitis C, causes hemolysis in a dose-dependent fashion. Its mechanism of red cell damage is unclear, but it may relate to nucleotide depletion. Other agents such as cyclosporine and tacrolimus may cause a microangiopathic hemolytic anemia due to endothelial damage (see section "Microangiopathic Hemolytic Anemia").

MICROANGIOPATHIC HEMOLYTIC ANEMIA

The microangiopathic hemolytic anemias are defined as disorders in which narrowing or obstruction of small blood vessels results in distortion and fragmentation of erythrocytes leading to hemolysis and subsequent anemia [36]. The hallmark finding on the blood smear is the schistocyte, a fragmented RBC (Fig. 112.1). It is essential that the intensivist recognize the differential diagnosis of microangiopathic hemolytic anemia as many of the diagnoses, some of which may be apparent given the patient's current or recent medical history, require prompt recognition and treatment (Table 112.9) [36,37]. If the underlying etiology of microangiopathic hemolytic anemia is in question, immediate hematology consultation is strongly recommended to evaluate for life threatening diagnosis such as thrombotic TTP.

TTP, once almost uniformly fatal, can now be treated effectively in the majority of patients with prompt recognition and initiation of therapeutic plasma exchange (TPE) [36–38]. The diagnosis should be suspected in any patient who presents with unexplained microangiopathic hemolytic anemia and thrombocytopenia [36–38]. The "classic pentad" of microangiopathic hemolytic anemia, thrombocytopenia, mental status changes, renal failure, and fever is present in fewer than 25% of patients at presentation. Only unexplained microangiopathic hemolytic anemia and thrombocytopenia are required to suspect the diagnosis; the clinical sequela are likely late manifestations of the disease [39].

Moake and others first noted unusually large von Willebrand factor (vWF) multimers in the plasma of affected patients and proposed them to be central in the pathophysiology of the disorder [40]. In the late 1990s, two groups reported that a vWF-cleaving protease (later termed ADAMTS-13, as a member of a disintegrin and metalloproteinase with thrombospondin components family of proteins) was found to be absent in familial TTP and inhibited by an antibody in the majority of cases of acquired TTP [41,42]. The absence of ADAMTS-13 was subsequently shown to prevent the breakdown and lead to the accumulation of ultra large molecular weight vWF multimers [40,43,44]. These ultra large vWF multimers efficiently bind to glycoprotein receptors on platelet surfaces leading to adhesion of platelets to the blood vessel endothelium and subsequently to small vessel occlusion affecting a variety of organs [38,40]. Hemolytic anemia occurs due to the mechanical shearing of RBCs as they transverse the turbulent and occluded microvasculature, thus leading to the classic findings of schistocytes seen on the peripheral blood smear (Fig. 112.1) [36,45].

TABLE 112.9

DIFFERENTIAL DIAGNOSIS OF MICROANGIOPATHIC HEMOLYTIC ANEMIA

- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Disseminated intravascular coagulation
- HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets)
- Preeclampsia
- Malignant hypertension
- Malfunctioning prosthetic heart valve with turbulent flow
- Severe vasculitis
- Scleroderma renal crisis
- Catastrophic antiphospholipid antibody syndrome
- Malignancy
- Intravascular foreign bodies
  - Left ventricular assist device
  - Intra-aortic balloon pump
- Drugs
  - Cyclosporine
  - Tacrolimus
  - Ticlopidine
  - Clopidogrel
  - Chemotherapeutic agents such as mitomycin C and gemcitabine

Clinical Manifestations

As discussed earlier, the clinical manifestations of TTP can be quite varied. Neurologic symptoms may range from subtle confusion to frank seizures or coma. Renal dysfunction may range from mild proteinuria or azotemia to acute renal failure. Occlusion in the blood vessels of the cardiac conduction system may lead to arrhythmias and sudden cardiac death. Pancreatitis has been described and should be considered in patients with abdominal pain. Fever is often noted. Any organ maybe affected leading to a wide range of symptoms.

Laboratory Features

Laboratory evaluation usually reveals a hemolytic anemia with at least (and often more than) 2 schistocytes or greater than 1% of RBCs per 100× field on microscopic exam (Table 112.4 and Fig. 112.1) [37,38]. Coagulation studies such as the activated partial thromboplastin time and the prothrombin time are typically normal, whereas they are usually prolonged in disseminated intravascular coagulation (DIC). The Coombs test is negative. Most cases of classic acquired TTP are associated with a severe deficiency of ADAMTS-13 (< 5%), and an inhibitory antibody can be demonstrated [41–43,45]. ADAMTS-13 results are often not available in real time, are not required to make the diagnosis, and should not routinely be used to make therapeutic decisions regarding the initiation of plasma exchange. ADAMTS-13 levels have prognostic value regarding the risk of relapse but are less useful in determining the likelihood of initial response to plasma exchange. Moderate decreases in ADAMTS-13 are not specific and may be seen in a variety of disorders including sepsis [43].

Schistocytes may be seen in conditions other than TTP (Table 112.9). These conditions usually have in common damage to the blood vessel endothelium, leading to the release of ultra large vWF multimers. The presentation of these syndromes may mimic TTP, although the hemolytic uremic syndrome (HUS) often presents with a primary component of renal failure [36]. Conditions other than TTP are not typically associated with a severe (< 5%) deficiency of ADAMTS-13 and TPE may not be effective, although it is often initiated if HUS is suspected [36,41].

The distinction between TTP and HUS may be difficult to make. Classic childhood HUS is usually preceded by hemorrhagic diarrhea caused by *Escherichia coli* 0157:H7. Atypical HUS as seen in adults may be difficult to differentiate from TTP. Typically, renal failure is more severe and extra renal manifestations are less or absent in HUS [36,38]. Thrombocytopenia and the presence of schistocytes may be more marked. ADAMTS-13 is not usually severely depressed in HUS, suggesting a different pathophysiology between these two related conditions [41]. Atypical HUS has been linked to uncontrolled activation of the complement system due to either congenital or acquired mutations or antibodies against various factors in the complement pathway [46]. As the ability to differentiate between TTP and atypical HUS is often unclear, prompt TPE is often initiated in atypical HUS, even though efficacy may be less as compared to TTP [36,38].

Treatment

TPE with fresh frozen plasma at a 1.0 to 1.5× plasma volume should be initiated as soon as idiopathic TTP is suspected [36,38,44,45]. A dual-lumen, large bore, dialysis-type catheter is often needed for the procedure and should be promptly placed despite the coexisting thrombocytopenia. With prompt TPE, 80% to 90% of patients with classic TTP survive this once uniformly fatal disease [36–38]. The effectiveness of TPE is thought to be due to both the removal of an anti-ADAMTS-13 antibody and the replacement of ADAMTS-13 in donor fresh frozen plasma. If TPE is not readily available, FFP should be infused at a rate of 30 mL per kg per day while arrangements for TPE are made [44]. Randomized trials have supported the efficacy of TPE over simple plasma infusion which could become problematic given the large volume of FFP needed [45,47].

TPE should be continued until the platelet count and LDH have normalized for 2 days [39]. Plasma exchange is often tapered down to every other day upon remission, but this practice has not been critically studied and its efficacy in preventing relapse is uncertain. In refractory or relapsing patients, cryosupernatant plasma, devoid of vWF, should be considered [45,48]. Catheter-related infections should also be investigated and have been documented to lead to relapse. Immunosuppressants such as glucocorticoids and cyclosporine as adjuncts to plasma exchange have been used, but efficacy remains uncertain [36,38]. Aspirin has also been used for its antiplatelet effects but is often avoided until the platelet counts begin to rise [39]. Platelet transfusion is generally avoided, as it was thought to exacerbate the disease although recent data calls this into question [49].

In small case reports and case series, rituximab has been found to be effective in relapsing and refractory cases and should be considered [50,51]. Recombinant ADAMTS-13 is under development and may prove to be effective in the future.

Disseminated Intravascular Coagulation

Although microangiopathic hemolytic anemia may be present in patients with DIC, typically the thrombotic or bleeding manifestations of DIC are more clinically significant. DIC, which is often due to an underlying serious or catastrophic event such as septicemia or an obstetric emergency, will be covered in greater detail in Chapters 108 and 109.

Other Causes of Microangiopathic Hemolytic Anemia

The differential diagnosis of microangiopathic hemolytic anemia includes the other diagnoses listed in Table 112.9. Appropriate consultation and treatment should be pursued dependent on the most likely diagnosis.

HEMOGLOBINOPATHIES

Sickle Cell Anemia

Sickle cell anemia results from the presence of a point mutation leading to an amino acid substitution (valine for glutamic acid) in the sixth position of the beta chain of hemoglobin. An unstable form of hemoglobin (hemoglobin S) is produced which polymerizes in the setting of dehydration or hypoxia, a term referred to as sickling. The sickling of red cells is responsible for a variety of clinical conditions including extremely painful episodes in the back and extremities. Patients may be symptomatic if they are homozygous for hemoglobin S; if they are compound heterozygotes for hemoglobin S, hemoglobin C, hemoglobin D, and hemoglobin E; or if they also have concomitant beta thalassemia. The most common complications of sickling disorders leading to ICU admission are listed in Table 112.10.

Transfusion. Although patients with sickling disorders are nearly always anemic, transfusions are not indicated for hemodynamically stable anemia, routine vasoocclusive crisis, routine

TABLE 112.10

CRITICAL CARE COMPLICATIONS OF SICKLE CELL DISEASE

Acute chest syndrome
Acute stroke
Acute cholecystitis
Congestive heart failure
Hyperhemolysis
Pulmonary hypertension
Sepsis
Severe aplastic crisis
Delayed transfusion reaction

pregnancies, or simple surgical procedures that do not require general anesthesia. In general, hematology consultation is indicated if transfusion is considered, as the need for transfusion usually suggests a more complicated clinical scenario. Transfusion therapy can be simple, chronic, or performed via RBC exchange. Simple transfusion involves infusion of a sufficient volume of red cells to improve tissue oxygenation. Chronic simple transfusions are primarily used to prevent stroke recurrence. RBC exchange, performed (where available) via erythrocytapheresis using a noncollapsible, large bore, dialysis-type catheter, involves the removal of the patient's hemoglobin S red cells, followed by replacement of RBCs from a non–hemoglobin S donor targeting a final hemoglobin no higher than 8 to 10 g per dL with hemoglobin S less than 30%. RBC exchange is often used in the management of acute stroke or severe acute chest syndrome (ACS) as a more rapid and efficient way to remove hemoglobin S and improve oxygen delivery. Alternatively, manual exchange transfusion involves removing 500 cc of blood, followed by infusion of 300 cc normal saline, followed by another 500 cc removal of blood, and subsequent transfusion of 4 to 5 units of packed red cells [52]. Care should be taken to keep the end hemoglobin value no higher than 10 g per dL to minimize the risk for hyperviscosity.

Alloimmunization, typically to the Rh (E, C), Kell (K), Duffy (Fya, Fyb), and Kidd (Jk) antigens, occurs in up to 30% of patients [53]. Alloimmunization can be minimized by transfusing red cells that have been phenotypically matched for these red cell antigens. If phenotypically matched units are not available, crossmatched red cell units that are negative for C, E, and Kell are recommended.

Acute Chest Syndrome

Pulmonary complications frequently cause significant morbidity and mortality in patients with sickling disorders and are a common reason for ICU admission. Among the pulmonary complications, the ACS is among the most frequently observed in the ICU setting.

Clinical Features. ACS can be defined by a constellation of fever, hypoxemia, chest pain, leukocytosis, and new pulmonary infiltrate in a patient with a sickling disorder [54]. Although most common in patients homozygous for hemoglobin S, ACS can also be seen in decreasing frequency in patients with hemoglobin SC disease and S/β+ thalassemia. Importantly, the clinical definition of ACS does not indicate a specific etiology. ACS can be caused by infection, thrombosis, fat embolism, or any combination of these conditions. A large multicenter study showed that a specific cause of ACS could be identified in more than 50% of patients studied [55]. The most common etiologies observed were fat embolism and infection. Specific etiologies of ACS from this study of 671 episodes are listed in Table 112.11.

TABLE 112.11

CAUSES OF THE ACUTE CHEST SYNDROME IN A 30-CENTER STUDY

Cause	Percentage
Fat embolism, with or without infection	8.8
Chlamydia	7.2
Mycoplasma	6.6
Virus	6.4
Bacteria	4.5
Mixed infections	3.7
Legionella	0.6
Miscellaneous infections	0.4
Infarction	16.1
Unknown	45.7

Adapted from Vichinsky EP, Neumayr LD, Earles AN, et al: Causes and outcomes of the acute chest syndrome in sickle cell disease. *N Engl J Med* 342:1855–1865, 2000.

Physiologic Markers. Secretory phospholipase A2, a potent inflammatory mediator, has been implicated as a cause of lung damage in patients with ACS [56], and serum levels may be predictive of impending ACS [57]. In addition, circulating activated endothelial progenitor cells have been proposed as a potential etiology of ACS [58].

Treatment. Treatment of ACS depends in part on the clinical presentation. If the sputum Gram stain suggests infection with a particular organism, targeted antibiotic therapy should be initiated without delay. Interestingly, although pneumococcus is a frequent cause of infection in children with ACS, it is much less common in adults, in whom mycoplasma is more frequently implicated [54]. However, when an infectious etiology of ACS is suspected, empiric coverage for pneumococcus remains appropriate. In addition, because of the high mortality associated with ACS, empiric antibiotic coverage for mycoplasma and chlamydia should also be strongly considered. Maintaining hydration and oxygenation during episodes of ACS are imperative to prevent further sickling. However, fluids must be administered carefully to avoid fluid overload. There is no data to support the routine use of anticoagulants in ACS, and in the absence of data, this practice should be avoided.

Patients with ACS and hypoxia ($PO_2 < 75$ mm Hg) should be transfused red cells by either simple or exchange transfusion [59]. One small single-institution study found no difference between the two transfusion modalities [60]. Clinically, decisions between these two strategies are usually based on the degree of hypoxia, the pace of respiratory failure, as well as other comorbidities. Red cell exchange transfusion may be favored in the more severe or rapidly progressive cases and in critically ill patients with hemoglobin SC disease because such patients typically have baseline hemoglobin levels in the 10 to 11 g per dL range. In addition to providing a source of oxygen delivery, exchange transfusion also decreases levels of inflammatory mediators such as soluble vascular cell adhesion molecule-1 [61].

Acute Stroke

Stroke is one of the most morbid complications of sickle cell disease, with a prevalence of more than 20% in some series [62]. In addition to overt stroke, more than 60% of patients with sickle cell disease have evidence of brain damage from occult

infarction that is incidentally found on magnetic resonance imaging [63]. The pathophysiology of stroke in sickle cell patients is complicated. Stroke is related to nitric oxide depletion, hypercoagulability, and abnormalities of the major cerebral arteries. Unfortunately, stroke recurrence is common with more than 50% of cases occurring within 36 months following the initial event [64]. The presence of constricted cerebral arteries with collateralization (moyamoya syndrome) is associated with recurrent stroke and may be alleviated by surgical vascular bypass [65]. Although transcranial Doppler measurement of blood velocity has predictive value for stroke in pediatric patients with sickle cell disease, the measurement of cranial blood flow velocity is less able to stratify the risk of stroke for adults [66].

Treatment. Although there have been no specific trials addressing the issue, antiplatelet agents can be used in the treatment of acute stroke in adults with sickle cell disease, similar to patients without sickle cell disease [67]. Although there are no randomized trials, retrospective studies suggest that the use of red cell exchange transfusion to increase oxygen carrying capacity to the brain in the setting of acute stroke may be of some benefit [59]. For acute stroke in patients with sickle cell disease, emergent red cell exchange transfusion to reduce hemoglobin S to less than 30% has been recommended by some experts [68]. Similarly, consensus opinion suggests that conventional angiography can be used in sickle cell patients suspected of having an aneurysmal subarachnoid hemorrhage [59]. Because of the osmotic dye load which might increase intracerebral sickling, experts also suggest exchange transfusion prior to angiography [59]. Acute retinal artery occlusion can be considered as an ophthalmic stroke. The exact pathophysiology of retinal artery occlusion in sickle cell disease and risk factors for the condition are not known [69]. Similarly, there is scant data on the treatment of retinal artery occlusion in sickle cell anemia. At this time, it is reasonable for sickle cell patients presenting with acute thrombotic stroke or acute retinal artery occlusion to undergo red cell exchange transfusion. In addition, antiplatelet agent administration appears reasonable.

Acute Cholecystitis

Patients with hemolytic disorders, including sickle cell disease, form gallstones composed of the insoluble salt, calcium bilirubinate. For sickle cell patients presenting with acute cholecystitis, laparoscopic cholecystectomy appears safe and effective [70]. A prospective trial supports the idea that most sickle cell patients undergoing cholecystectomy should receive transfusion support [71]. A randomized trial has suggested that simple preoperative transfusion to a hemoglobin level of 10 g per dL is not associated with more complications than preoperative red cell exchange transfusion to a target hemoglobin S less than 30% [72]. In addition, simple transfusion is associated with a lower rate of alloantibody formation, as fewer units of RBCs are transfused. The use of postoperative incentive spirometry is strongly encouraged due to a decreased incidence of ACS [73].

Pulmonary Hypertension

Pulmonary hypertension is a recently recognized cause of morbidity and mortality in sickle cell disease occurring in more than 30% of patients and conferring an increased death rate ratio of 10.1 [74]. Pulmonary hypertension may be secondary to nitric oxide scavenging by free hemoglobin released during hemolysis. Such scavenging can lead to synthesis of vasoconstrictors such as vascular-cell adhesion molecule 1 and E-selectin. Hemolysis also leads to the release of arginase from hemolyzed red cells, reducing nitric oxide synthesis. The formation of reactive oxygen and nitrogen species catalyzed by free hemoglobin may also lead to pulmonary vasoconstriction. Pulmonary hypertension, in conjunction with high cardiac output, is a major cause of congestive heart failure in patients with sickle cell disease.

The management of patients with sickle cell disease and pulmonary hypertension remains controversial. Some authors have noted a decreased incidence of pulmonary hypertension in retrospective studies of patients treated with hydroxyurea [75], but this finding is not universal. A small study found that therapy with sildenafil improved exercise capacity in patients with sickle cell disease and pulmonary hypertension [76]. However, a recent trial using sildenafil in children with sickle cell disease and pulmonary hypertension was prematurely suspended due to an increase incidence of adverse events including painful crisis. Speculation exists that endothelin antagonists, such as bosentan, may also be effective in reducing pulmonary pressures, although prospective trials are lacking. Such is also the case for epoprostenol and oral arginine [77].

Currently, there is insufficient evidence in the medical literature to suggest specific treatment strategies for patients with sickle cell disease and pulmonary hypertension. At a minimum, conservative management including oxygen therapy to treat hypoxia and aggressive treatment of right heart failure are recommended.

Hyperhemolysis

Patients with hyperhemolysis, characterized by a lower posttransfusion hemoglobin compared with the pretransfusion value, present with profound anemia and hemolysis despite red cell transfusion support [78]. The pathophysiology of hyperhemolysis in sickle cell disease remains unclear but may be related to a combination of bystander hemolysis, suppression of erythropoiesis, and destruction of RBCs due to contact lysis via activated macrophages [79]. There are case reports supporting the use of IVIG and corticosteroids in addition to transfusion to maintain enough RBCs to support the circulation [80]. Erythropoietin administration may also be of benefit in cases where the reticulocyte count is inadequate. Although hyperhemolysis can recur, typically it occurs as an isolated event. Prompt recognition is important to avoid life-threatening anemia in the setting of continued erythrocyte transfusion.

Aplastic Crisis

Aplastic crisis in sickle cell disease is usually secondary to either folic acid deficiency or infection with parvovirus B19. Aplasia secondary to folic acid deficiency is more common in late pregnancy when folic acid requirements are increased. Infection with parvovirus can be accompanied by marked marrow necrosis [81]. Treatment of parvovirus infection–induced aplasia in immunocompetent individuals is supportive and resolves upon clearance of the virus.

Sepsis

Because patients with sickling disorders are functionally asplenic, infection remains a common reason for hospitalization. Pneumonia is the most common infection and may be due to pneumococcal species, especially if the patient did not receive appropriate immunizations. Treatment of patient with sickle cell disease and sepsis parallels the treatment of similar patients without a coexistent hemoglobinopathy. Broad-spectrum antibiotics which can later be tailored to the most likely organism should be administered immediately. Adequate hydration must be maintained during an infectious episode to prevent further sickling of erythrocytes. Organisms responsible for sepsis in the sickle cell population can be found in Table 112.12. Consideration of immunization status is important when considering the most likely organism.

TABLE 112.12

ORGANISMS RESPONSIBLE FOR BLOOD-BORNE INFECTIONS IN PATIENTS WITH SICKLING DISORDERS

Gram-positive cocci
Staphylococcus aureus
Coagulase-negative staphylococci
Streptococcus pneumoniae
Viridans Streptococci
Enterococci
Streptococcus bovis
Gram-negative bacilli
Acinetobacter baumannii
Escherichia coli
Klebsiella spp
Anaerobes
Bacteroides spp
Fusobacterium sp
Fungi

Adapted from Chulamokha L, Scholand SJ, Riggio JM, et al: Bloodstream infections in hospitalized adults with sickle cell disease: a retrospective analysis. *Am J Hematol* 81:723–728, 2006.

Thalassemia

Patients with thalassemia can develop high output heart failure that can lead to ICU admissions. Treatment of heart failure in thalassemic patients is similar to the management of heart failure in other patient populations including the use of diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers. Chelation therapy with deferasirox is recommended in patients with thalassemia major and iron overload especially if iron overload has caused cardiac toxicity. Transfusion support is required in symptomatic anemia. Unless a coexistent hemoglobinopathy is present, stroke, ACS, and other common complications of sickle cell disease are not typically seen.

Hemolytic Transfusion Reactions

Patients may experience hemolytic transfusion reactions that are either immediate (acute) or delayed. Acute hemolytic transfusion reactions (AHTRs) typically manifest with a feeling of impending doom. Subsequently, back pain, hypotension, red urine, and shock develop. Renal failure due to the massive hemoglobin load may occur, and DIC often ensues. Between the years 1990 and 1992, the majority of the 150 preventable transfusion-related fatalities reported to the Food and Drug Administration (FDA) were due to ABO-incompatible RBC transfusions leading to an AHTR [82–84]. Indeed, AHTR is typically the result of human error, in specimen collection, labeling, or transfusion [83]. Errors within the laboratory are much less common. Although this dramatic presentation is classic, it is important to note that a rise in temperature of 1°C above baseline may be the sole initial presentation of a hemolytic transfusion reaction and necessitates the cessation of transfusion of that unit of red cells and initiation of workup for transfusion reaction. In the case of an immediate hemolytic transfusion reaction, hemoglobinuria and hemoglobinemia may be seen, and reaction between the remnant of the transfused unit and the patient's pretransfusion serum can be identified. Treatment consists of stopping the transfusion as soon as the reaction is suspected, hydration, forced diuresis, and maintenance of blood pressure.

Delayed hemolytic transfusion reactions (DHTRs) typically present 1 to 4 weeks after transfusion of a unit of red cells. The patient may present with fatigue, jaundice, pallor, or red- or tea-colored urine. Patients with sickling disorders may come to medical attention due to a new or worsening pain crisis. The hemoglobin will be lower than that seen posttransfusion. The LDH and bilirubin will be increased, the reticulocyte count will likely be elevated, and the antibody screen will be positive, and a new alloantibody often identified. The DHTR is typically due to mismatches of non-ABO red cell antigens. Patients should be issued a card stating the antigen to which they have made a new alloantibody and told to present this card prior to all future transfusions. This is especially important in cases of antibodies to the Kidd antigen, as these alloantibodies are typically transient and may not be detectable on future antibody screens.

Glucose 6-Phosphate Dehydrogenase Deficiency

G6PD deficiency, a sex-linked trait primarily affecting men most commonly of African American or Mediterranean descent, is the most common erythrocyte enzyme defect in the world [85]. G6PD is necessary to maintain glutathione in its reduced state in the erythrocyte. Patients deficient in this enzyme are subject to oxidative hemolysis when exposed to certain drugs and toxins, or during episodes of infection. A sample list of drugs to be avoided in G6PD-deficient patients is provided in Table 112.13. Because acute infection makes oxidative hemolysis more likely, there has been confusion about the safety of certain drugs in G6PD-deficient patients. A list of drugs that can be safely administered to G6PD-deficient patients is shown in Table 112.14. A more exhaustive drug list can be found at many Web sites dedicated to G6PD deficiency (ex. www.g6pd.org). G6PD deficiency is seldom a major issue in critically ill patients because the anemia is typically not severe, and the patients are closely monitored. However, in solid organ transplant recipients who are exposed to oxidant drugs such as trimethoprim–sulfamethoxazole or dapsone, the diagnosis should be strongly considered in the setting of a new hemolytic or unexplained acute anemia [86].

In the more common African American variant of G6PD, enzyme levels are elevated in young reticulocytes, and therefore measurement of this enzyme should not be attempted in the

TABLE 112.13

DRUGS TO BE AVOIDED IN G6PD-DEFICIENT PATIENTS

Dapsone
Methylene blue
Nalidixic acid
Nitrofurantoin
Phenazopyridine
Primaquine
Sulfacetamide
Sulfanilamide
Sulfapyridine
Toluidine blue
Urate oxidase

Note: List is not intended to be all inclusive.
Adapted from Lichtman MA, Beutler E, Kipps TJ, et al: Williams hematology, 7th ed. New York: McGraw-Hill Medical, 2006.

TABLE 112.14

DRUGS THAT ARE SAFE IN G6PD-DEFICIENT PATIENTS

Acetaminophen
Acetylsalicylic acid
Ascorbic acid
Chloramphenicol
Chloroquine
Colchicine
Diphenhydramine
Isoniazid
Phenytoin
Procainamide
Pyrimethamine
Quinine
Streptomycin
Sulfadiazine
Sulfamethoxazole
Trimethoprim
Vitamin K

Note: List is not intended to be all inclusive.
Adapted from Lichtman MA, Beutler E, Kipps TJ, et al: Williams hematology. 7th ed. New York: McGraw-Hill Medical, 2006.

setting of an acute hemolytic episode, where the majority of circulating red cells are young.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disease in which an abnormal stem cell clone gives rise to red cells, white cells, and platelets that lack proteins which are normally attached to the cell surface by a glycerophosphatidylinositol (GPI) anchor. Among these proteins are CD55 and CD59, which are responsible for inactivating complement on the surface of red cells. PNH cells are therefore more susceptible to complement-mediated lysis [87]. Patients with PNH may come to the attention of the intensivist with complications such as hemolysis, pancytopenia, arterial, or venous thrombosis (including the Budd–Chiari syndrome/hepatic vein thrombosis). Patients may also develop pancytopenia due to marrow hypoplasia, as there is an association with primary bone marrow disorders such as aplastic anemia, myelodysplastic syndrome (MDS), and acute myelogenous leukemia [88,89].

Flow cytometry showing the absence of GPI-linked surface molecules CD55 and CD59 on erythrocytes and granulocytes has supplanted older testing (such as the Ham's test) for the diagnosis of PNH [88]. Eculizumab has been FDA approved for the treatment of hemolysis due to PNH. Patients treated with eculizumab show markedly lower rates of hemolysis and also thrombosis [90–94] but are at increased risk for infection with meningococcus, requiring immunization prior to use [88].

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is an autosomal dominant disorder, of red cell membrane skeletal proteins leading to a lack of anchoring of the red cell lipid bilayer to its skeletal backbone [95–97], leading to a characteristic spherocytic shape. Patients have lifelong hemolysis which is often well compensated. However, with even mild infections, the hemolysis can accelerate, and the patient can become more anemic. Splenomegaly is present in many patients and splenic rupture may occur after trauma. Patients with HS may present with an aplastic crisis manifested by severe reticulocytopenia and anemia often due to parvovirus B-19 infection which transiently suppresses the bone marrow's ability to produce red cells and compensate for the accelerated hemolysis [97,98]. The Coombs test will be negative and should be used to differentiate HS from warm autoimmune hemolytic anemia, which can present similarly. RBC transfusion may be administered to patients with aplastic crisis.

Hemolysis from Infectious Agents

Certain infectious pathogens cause hemolysis that can be severe or life threatening. Malaria is prototypic; infection with falciparum malaria is known as blackwater fever, due to the massive hemolysis caused by this agent. *Babesia microti* is another intracellular parasite that can lead to hemolysis. It is carried by the same tick as Lyme disease and can look like malarial forms on peripheral smear. *Bartonella bacilliformis*, the agent responsible for Oroya fever, and *Verruca peruvianis*, an extracellular parasite, can lyse red cells leading to dramatic hemolysis. In endemic regions of the world, these organisms are leading causes of hemolysis in critically ill patients. The toxin of *Clostridium welchii*, an agent of gas gangrene, may cause severe hemolysis. The bacterium produces a lysolecithinase, which attacks the red cell membrane bilayer. *Clostridium perfringens*, another agent causing gas gangrene, also leads to hemolysis via the action of phospholipases produced in its exotoxin [99]. In certain cases, the hemolysis can be severe enough to produce a disparity between the hemoglobin and the hematocrit. This infectious complication typically follows bowel or gynecologic surgery.

Hemolysis Associated with Chemical and Physical Agents

Arsenic, especially arsine gas, can lead to hemolysis, as it can elevate levels of copper in the blood. Wilson's disease, which is a disorder of copper metabolism, may present with hemolysis as part of its clinical picture [100]. Some dialysis centers have had difficulty with copper contamination of their water supply, leading to severe hemolysis [101]. Insect and spider bites, especially the bite of the brown recluse spider (*Loxosceles reclusa*), can lead to hemolysis, as can certain snakebites [102]. Severe burns can lead to hemolysis, since the red cell membrane is sensitive to temperatures more than 55°C.

Other Causes of Anemia in the Critical Care Setting

Iron deficiency leads to a hypoproliferative anemia due to the inability to synthesize hemoglobin. Iron deficiency may be caused by chronic blood loss, decreased iron intake (either from dietary reasons or from iron malabsorption as occurs in celiac sprue or following gastrointestinal bypass), or both. In the ICU, red cell transfusion is the most immediate way to correct the anemia, but in patients with a low hemoglobin but no hemodynamic compromise, oral or intravenous iron is preferred. Parenteral iron may be preferred in iron-deficient patients who have undergone gastrointestinal bypass, cancer patients, those who suffer from functional iron deficiency, patients undergoing treatment with erythropoietin, or patients with chronic kidney disease [103–106]. Iron dextran, iron sucrose, iron gluconate, and ferumoxytol are all available for intravenous use. The newer formulations of iron dextran have a lower rate of severe allergic reactions compared with older dextran preparations, but the incidence continues to remain higher than with the newer nondextran iron preparations [107–114].

TABLE 112.15

MECHANISMS OF THE ANEMIA OF CHRONIC DISEASE/CRITICAL ILLNESS

Blood loss
Phlebotomy
Active bleeding
Decreased red cell production
Decreased production of erythropoietin
Blunted response to erythropoietin
Sequestration of iron through up regulation of hepcidin
Renal dysfunction
Increased red cell destruction
Reduced red blood cell deformability

The iron deficit is calculated by the following formula: (desired hemoglobin − actual hemoglobin) × (weight in pounds) + storage iron. Storage iron is estimated at 1,000 g for men and 600 mg for women.

Megaloblastic Anemia

Megaloblastic anemia is a rare cause of anemia in the ICU but should be suspected in the individuals presenting with a macrocytic, hypoproliferative anemia (high MCV, low reticulocyte count) (Table 112.5). Vitamin B_{12} and folic acid levels should be measured, but accuracy may be affected in the acute setting. The measurement of homocysteine and methylmalonic acid (MMA) is a more sensitive way to asses for these nutritional deficiencies but can also be altered in the critically ill patient [115]. Typically, both homocysteine and MMA are elevated in B_{12} deficiency, while homocysteine alone is elevated in folic acid deficiency. Elevation of homocysteine and MMA may be the first laboratory signs of subclinical B_{12} deficiency. The peripheral smear may show oval macrocytes and hypersegmented neutrophils. Other anemias which are hypoproliferative and macrocytic include the MDS, aplastic anemia, the anemia of hypothyroidism, and liver disease (Table 112.5).

Anemia of Chronic Disease (ACD)/Inflammation

The anemia of chronic disease/inflammation is common in the ICU and its etiology is multifactorial (Table 112.15) [1]. Once thought to occur over weeks to months, the ACD has been shown to occur in less than a week and is thus thought to be a major contributor to anemia in critically ill patients [1,116]. Several studies have shown elevated levels of cytokines such as tumor necrosis factor-alpha; interleukin-6; C-reactive protein; and interferons alpha, beta, and gamma in ACD [1,117,118]. This cytokine response has been shown to inhibit erythropoietin production, blunt the erythropoietic response, and play a central role in iron metabolism, leading to the sequestration of iron. Iron metabolism is primarily mediated by the antimicrobial peptide hepcidin, which impairs the ability to export iron from gut epithelial cells and hepatocytes into the bloodstream [119]. Hepcidin is upregulated in the ACD, leading to the sequestration of iron. In the ACD, the serum iron (Fe), total iron-binding capacity (TIBC), and percentage iron saturation (iron/TIBC) are typically low. Ferritin, an acute phase reactant, is often normal or elevated, as opposed to iron deficiency where it is low. Renal failure is common in the ICU and also may contribute to the ACD, especially when progressive [1,120]. Increased red cell destruction has also been noted in the ACD due to decreased RBC deformability [1].

CONCLUSION

As demonstrated in this chapter, anemia is exceedingly common in the critical care setting, but its etiology remains very diverse. A rational approach to the evaluation of anemia includes review of the white blood count, platelet count, MCV, reticulocyte count, peripheral blood smear, and any prior CBCs that may be available. If hemolysis is suspected, LDH, bilirubin, and haptoglobin will provide additional information to support or refute this diagnosis. A Coombs test is often sent if the etiology of hemolysis remains in question. As highlighted in the chapter, certain causes of anemia such as blood loss, microangiopathic hemolytic anemia, complications of sickle cell disease, hemolysis from drugs as well as foreign devices, and ACD are seen with increased frequency in critically ill patients and should be considered in the ICU patient population. Specific treatment recommendations are based on the underlying diagnosis. Minimization of the volume and frequency of blood draws is essential. Conservative transfusion thresholds are increasingly being used in the absence of hemodynamic compromise or acute blood loss. The role of ESAs has been investigated but remains uncertain. If the etiology of the anemia remains obscure, or the management of an underlying diagnosis remains uncertain, hematology consultation is recommended.

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CHAPTER 113 ■ THERAPEUTIC APHERESIS: TECHNICAL CONSIDERATIONS AND INDICATIONS IN CRITICAL CARE

THERESA A. NESTER AND MICHAEL LINENBERGER

TECHNICAL RATIONALE AND INSTRUMENTS

Apheresis means *to remove*. Apheresis instruments are designed to separate whole blood into its component parts to selectively remove one component and return the remaining components to the patient. By processing one or more blood volumes, a significant amount of pathologic solutes or cells may be removed while the intravascular compartment remains relatively euvolemic. In an exchange procedure, replacement fluid or blood is given back to the patient to allow plasma or red cells to be removed. With any apheresis procedure, some type of anticoagulant is added to the circuit to ensure that blood flows freely.

Centrifugation apheresis instruments use either a continuous or a discontinuous flow method to deliver blood to the separation device where blood cells and plasma are differentially sedimented according to their specific gravity. Continuous flow methods draw blood into the extracorporeal circuit, separate blood into components in the centrifugation chamber,

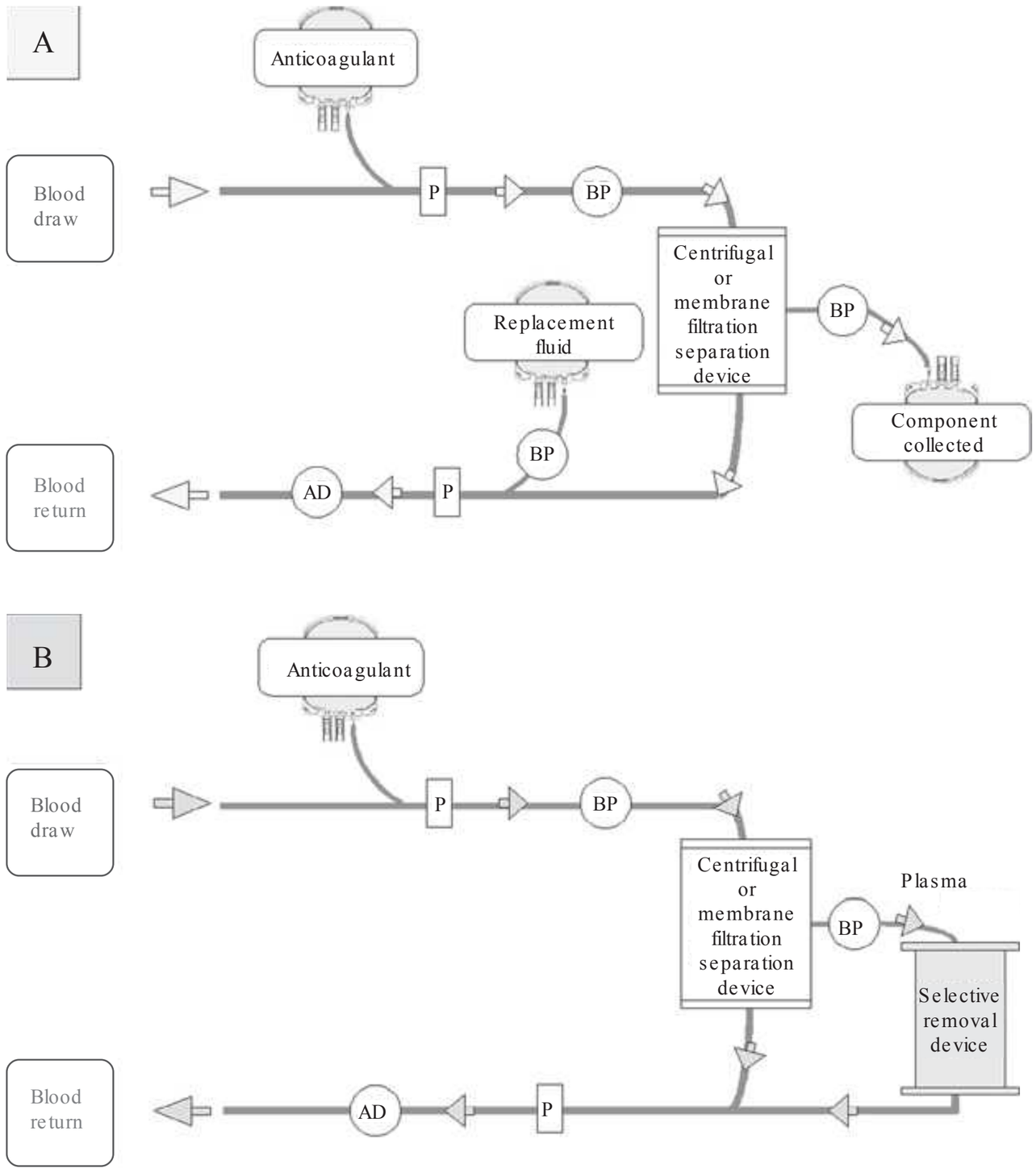

FIGURE 113.1. A: Basic circuitry and instrumentation of component removal in a therapeutic apheresis procedure. Anticoagulant is added to the patient's blood as it is drawn and pumped to the separation device. The component to be collected is pumped from the device to a collection bag, and the remainder of the blood is returned, along with appropriate replacement fluid, to the patient. **B:** Circuitry and instrumentation for selective removal of pathogenic substance from the patient's plasma. The patient's anticoagulated blood is pumped to the separation device, and separated plasma is then delivered to the selective removal device. The purified plasma is then combined with the cellular portion of the patient's blood and returned to the patient. AD, air detector; BP, blood pump; P, pressure monitor. [From Linenberger ML, Price TH: Use of cellular and plasma apheresis in the critically ill patient: part 1: technical and physiological considerations. *J Intensive Care Med* 20:18–27, 2005, with permission.]

divert the unwanted component into a collection bag, and return nonpathologic components to the patient without interruption (Fig. 113.1). Dual venous/catheter access is required for these procedures. Discontinuous, or intermittent, flow methods accomplish the same steps but draw, process, and return a discrete amount of blood extracorporeally before another discrete volume of blood is removed. Discontinuous procedures take a longer time than continuous procedures but require only single vein/catheter access [1].

Some apheresis instruments, predominantly used in Asia and Europe, use a membrane filtration technique to isolate plasma. The extracorporeal membrane consists of either a flat plate or a hollow fiber with a pore size that excludes cellular components from the filtrate. The plasma that is separated in the instrument is diverted for disposal or treatment, while the other blood components are returned to the patient [2].

Specialized columns and instruments have been developed over the years to treat separated plasma, with the goal of selectively removing pathogenic proteins or other solutes [3–8]. One example is hypercholesterolemia therapy. Two different columns are approved for patients with familial hypercholesterolemia who have failed combination drug therapy. The heparin-induced extracorporeal low-density lipoprotein (LDL) precipitation (HELP) system and Liposorber LA-15 system target the removal of LDLs from separated plasma [4]. Additional columns and systems have been tested and used outside the United States [5]. These include a dextran-sulfate column to remove anti-DNA and anticardiolipin antibodies and immobilized polymyxin B or other adsorbers to remove inflammatory cytokines and mediators of sepsis [6–8]. One specialized methodology, called extracorporeal photopheresis (ECP), involves isolating peripheral white blood cells by leukapheresis, treating the cells with a psoralen drug, and exposing them to ultraviolet A light before returning the photoactivated cells to the patient [9]. A dedicated instrument approved by the Food and Drug Administration (FDA) is used to perform ECP, which is beneficial for some patients with cutaneous T cell lymphoma, graft-versus-host disease after hematopoietic stem cell transplantation, systemic sclerosis, and solid organ transplant allorejection. Although ECP is usually an elective procedure, a critically ill patient may undergo treatment as part of a multimodality therapeutic approach.

PHYSIOLOGIC PRINCIPLES

The effectiveness of an apheresis procedure in reducing a plasma molecule or cellular component depends on two factors: (a) the distribution of that component between the intravascular and extravascular space and (b) the rate of regeneration of the component [10]. For solutes that move freely between intravascular and extravascular compartments, complete reequilibration between the compartments occurs at approximately 48 hours after a plasma exchange. Circulating blood cells also traffic between sites of vascular margination and/or splenic sequestration and this, in turn, can affect the efficiency of a therapeutic cytapheresis procedure.

The rate of intravascular regeneration of a pathologic solute or blood cell population after apheresis also depends on the rates of synthesis or production and decay or cell death. Plasma exchange typically removes large molecules at a rate that greatly exceeds their natural synthetic rate; thus, a simple one-compartment mathematical model is used to predict the depletion of soluble plasma substances. Assumptions of

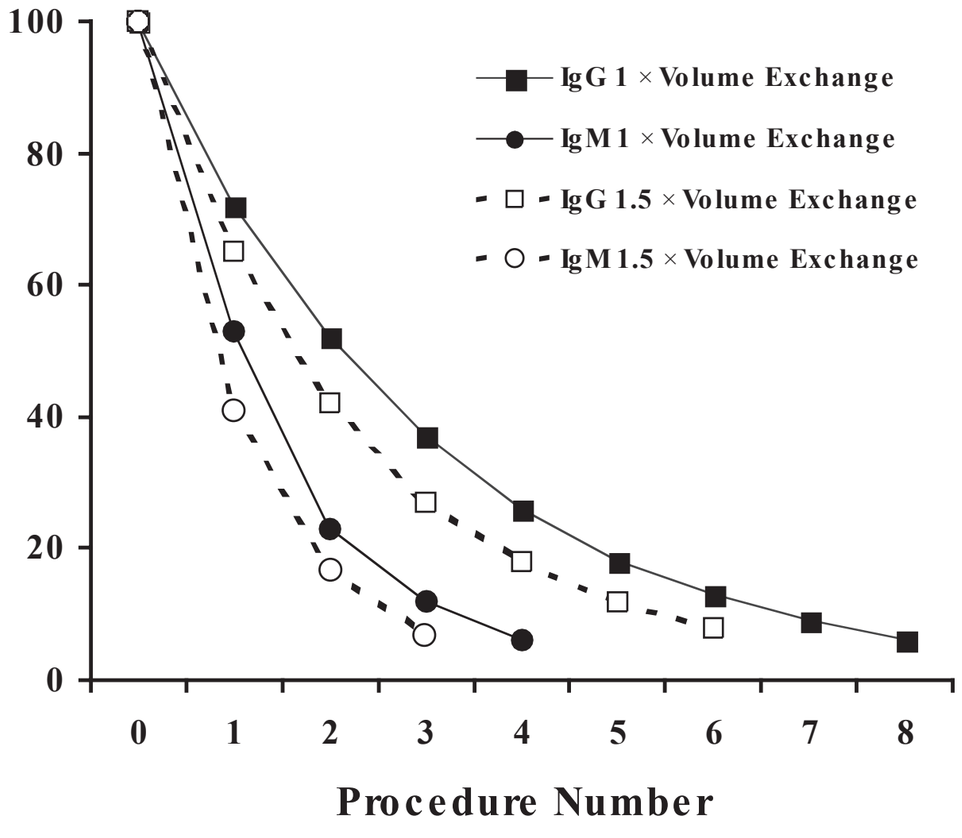

FIGURE 113.2. Hypothetical depletion of whole body immunoglobulin (Ig) levels by therapeutic plasma exchange. The 1-compartment model predicts that approximately 60% of the soluble substance will be removed from the plasma with a 1× plasma volume therapeutic exchange, and approximately 80% will be removed with a 1.5× volume exchange. Because roughly 50% of IgG distributes to the extravascular space, reequilibration between the intravascular and extravascular compartments occurs between sequential procedures, and 6 or 7 1× volume exchanges are needed to deplete whole body IgG to less than 10% of the pretreatment level. By comparison, IgM is predominantly intravascular, and, therefore, only 3 or 4 1× volume exchanges are needed to deplete whole body IgM to less than 10%. By increasing the processing to 1.5× plasma volumes, the same therapeutic goal would require three procedures to deplete IgM and five procedures to deplete IgG. [From Linenberger ML, Price TH: Use of cellular and plasma apheresis in the critically ill patient: part 1: technical and physiological considerations. *J Intensive Care Med* 20:18–27, 2005, with permission.]

the model are that the plasma removed is replaced with a fluid devoid of the target substance, and that complete mixing of the replacement fluid with the remaining intravascular plasma volume occurs [10]. Figure 113.2 depicts the kinetics of removal and regeneration of plasma immunoglobulin G (IgG) and IgM after therapeutic plasma exchange (TPE). The reliability of the one-compartment model to predict removal of soluble substances may be limited by conditions that cause an expanded plasma volume, such as paraproteinemia, molecules with rapid synthetic rates, and situations where rebound IgG production occurs, such as in the setting of humoral solid organ rejection due to a preformed antibody [11].

The efficiency of cell depletion by cytapheresis is less predictable than soluble substance removal by plasma exchange. Factors that may hinder the prediction include a rapid rate of cell production, such as occurs with untreated acute leukemia; the propensity of the spleen to sequester abnormal circulating cells or platelets; and miscalculation of the plasma volume of the patient. In general, a cytapheresis procedure in which 1.5 to 2.0 blood volumes are processed can be expected to remove approximately 35% to 85% of the target cells [12].

ANTICOAGULATION AND FLUID REPLACEMENT

Citrate is the most commonly used anticoagulant for plasma exchange and cytapheresis procedures. Heparin is often used with ECP, specialized column extraction systems, and plasma membrane filtration. Current apheresis instruments limit both the anticoagulant (citrate or heparin) dose and rate of blood return based on the patient's total blood volume. The operator can also adjust the ratio of anticoagulant to whole blood being processed.

The acid-citrate-dextrose (ACD) solution effectively chelates free or ionized plasma calcium, thereby preventing coagulation of blood and plasma in the apheresis circuit. The precise decrease in ionized calcium in vivo during an apheresis procedure is difficult to predict, as this depends on dilution, metabolism, redistribution, and excretion of infused citrate [13]. Fluid replacement with fresh frozen plasma (FFP) or albumin may decrease the ionized calcium further because of citrate in the FFP or calcium binding by albumin. Ionized calcium may typically decrease by 23% to 33%, as measured during donor apheresis procedures [14].

Citrate does not produce an anticoagulant effect in vivo. The half-life in patients with normal renal and hepatic function is approximately 30 minutes. In a patient with severe liver disease, where citrate will not be as quickly metabolized, the operator should reduce the amount and/or rate of ACD used during an exchange. In critically ill patients needing plasma exchange, it is advised that ionized calcium be monitored and intravenous calcium replacement be provided as needed. Some apheresis services use protocols for the infusion of intravenous calcium gluconate or calcium chloride during all TPEs [15].

Continuous reinfusion of extracorporeal heparin during an apheresis procedure will affect the patient's hemostatic parameters. The effect is measurable until the drug is metabolized, usually within 60 to 120 minutes of finishing the procedure. For patients already therapeutically anticoagulated with heparin, the anticoagulation normally used with apheresis may be reduced or eliminated. The primary providers of critically ill patients must communicate with the apheresis team all information regarding systemic anticoagulation, coagulopathy, and contraindications to anticoagulation, especially when heparin is planned for a therapeutic procedure. It is particularly important to document if the patient has known or suspected heparin-induced thrombocytopenia.

Replacement fluid used in plasma exchange may consist of FFP, albumin, or saline. The type of fluid depends on (a) the patient's baseline hemostatic parameters, particularly fibrinogen; (b) the anticipated number and frequency of procedures; and (c) the condition being treated. For a patient with a neurologic illness, such as acute Guillain–Barré syndrome, 1 to 1.5 plasma volume exchanges are typically performed every other day with 5% albumin as replacement fluid. This regimen and schedule allows the fibrinogen level to recover between procedures. Alternatively, if a condition requires that plasma exchange be performed daily, some FFP replacement will likely be needed to maintain the patient's fibrinogen at a hemostatic level. For conditions where a plasma component is felt to be an important part of the therapy, such as with thrombotic thrombocytopenic purpura, FFP should comprise at least half of the replacement fluid [16]. In such cases, fibrinogen and other coagulation factors will not be depleted.

An apheresis instrument that uses a centrifugation technique must deliver a specific volume of packed red cells to the separation chamber to maintain the cell/plasma density gradient necessary for efficient selective extraction. The extracorporeal blood volume (ECV) necessary for this purpose varies according to the specifications of the instrument and disposable tubing kit and the hematocrit of the patient. The AABB (formerly American Association of Blood Banks) recommends that the ECV for a general procedure should not exceed 15% of a patient's total blood volume [17]. The implications for a therapeutic apheresis procedure can be illustrated by the following example. A 60-kg adult with a hematocrit of 40% has a total blood volume of: 60 kg × 70 mL per kg (the standard

conversion factor for an adult male) = 4,200 mL; and a red cell volume of 4,200 mL × 40/100 = 1,680 mL. If the instrument requires 200 mL of extracorporeal red cell volume, then the ECV required to deliver that 200 mL will be 200/1,680 = 0.12, or 12% of the total blood volume. If, however, the same patient has a hematocrit of 20%, the red cell volume will be 4,200 mL × 20/100 = 840 mL; and the required ECV will be 200/840 = 0.24 or 24% of the total blood volume, which exceeds the AABB safety limit. Allogeneic red cells are required when the ECV exceeds 15%. These are either given to the patient as a transfusion prior to the procedure (to increase their pretreatment red cell volume), or used to "prime" the apheresis circuit at the beginning of the procedure (and returned to the patient as part of the return fluid).

VASCULAR ACCESS

The type of vascular access required for therapeutic apheresis depends on the status of the patient's peripheral veins, the condition being treated, and the anticipated treatment schedule. The vein or catheter must be able to withstand negative pressures associated with inlet rates ranging from 30 to 150 mL per minute for the draw line and up to 150 mL per minute for blood being returned to the patient. For a patient needing only one exchange, it may be possible to use antecubital or forearm veins. A 16- to 18-gauge Teflon or silicone-coated steel, back-eye apheresis, or dialysis-type needle is required for the draw line. The patient ideally will be able to help by squeezing a ball during the exchange.

A large bore central venous catheter is often required for critically ill patients, especially those requiring daily procedures [18,19]. Temporary or long-term tunneled catheters for adults weighing more than 40 kg should be at least 10-French size (Table 113.1). Smaller diameter short-term catheters are acceptable for smaller adults and pediatric patients. Plastic central venous catheters such as those used for cardiac pressure monitoring are not adequate for the draw line because they collapse under the negative pressure generated from the high inlet flow rate. These catheters or a peripheral vein may be useful as return access under certain circumstances.

Peripherally inserted central venous catheter (PICC) lines and standard port-a-catheters are also not options for venous access. Subcutaneous ports with a reservoir-type chamber can accommodate flow rates required for some apheresis procedures, typically, chronic red blood cell exchanges rather than plasma exchanges. Recently, the FDA-approved needle used to access these ports was discontinued, and safety concerns related to the use of unapproved needles have been raised [20]. Arteriovenous fistulas created for dialysis access can be used for therapeutic apheresis. The critical care team should consult with the apheresis team prior to placing venous access for the procedure.

LIMITATIONS AND POTENTIAL ADVERSE EVENTS

When considering therapeutic apheresis, two limitations should be remembered. First, apheresis is not the same as dialysis. It is not usually possible to end a procedure with a large net negative fluid balance (i.e., >200 to 400 mL) because the deficit is colloid rather than crystalloid, and hypotension is likely to occur. A safe end fluid balance is plus or minus 10% to 15% of the total blood volume. In addition, it is not recommended that red cells be transfused during the apheresis procedure (other than at the start as a blood "prime") because the cell separation gradient and cell/plasma interface in the separation chamber may be disturbed. The second limitation is that the procedure is almost always an adjunctive, rather than definitive, therapy for the condition being treated. Thus, while apheresis can be performed on very ill patients, one must carefully consider the risks that are associated with hemodynamic instability, hematologic abnormalities, the need for vascular access, and the priorities for more urgent primary treatments.

Possible adverse complications related to therapeutic apheresis are shown in Table 113.2. Central line complications include procedure-related events, infection, and bleeding (Chapter 2). Citrate toxicity occurs in approximately 0.8% to 1.2% of therapeutic procedures [21]. Higher risk is associated with larger process volumes, longer procedure duration, nonphysiological bleeding, severe anemia, unstable vital signs, liver failure, alkalosis due to hyperventilation, and use of replacement fluid consisting of blood components that contain citrate as the anticoagulant [17,22]. Signs and symptoms of hypocalcemia can include a metallic taste in the mouth, muscle

TABLE 113.1

CATHETER RECOMMENDATIONS BASED ON PATIENT WEIGHT

Patient weight	Catheter name	Manufacturer	Size/Gauge
Percutaneous (nontunneled) catheters for short-term apheresis			
35–70 kg	Quinton Mahurkar	Kendall	10–11.5 Fr 12 Fr (triple lumen)
	Duo-Flow XTP	Medcomp	9 Fr
>70 kg	Quinton Mahurkar	Kendall	10–11.5 Fr 12 Fr (triple lumen)
	Hemo-Cath	Medcomp	11.5 Fr
Tunneled catheters for long-term apheresis			
35–70 kg	Quinton Permcath	Kendall	10 Fr
>70 kg	Hickman TriFusion	BARD	12 Fr (triple lumen)
	VasCath	BARD	
	Ash Split Cath	Medcomp	13 Fr
	Mahurkar Cuffed	Kendall	14 Fr
	TAL PALINDROME	Kendall	13.5 Fr 14.5 Fr

Fr, French.

TABLE 113.2

POSSIBLE ADVERSE EFFECTS OF THERAPEUTIC APHERESIS

Central venous catheter-associated complications
Signs and symptoms of hypocalcemia and/or hypomagnesemia
Hypotension related to vasovagal reactions or fluid shifts
Transfusion reactions
Altered hemostatic parameters
Bradykinin reaction in patients on ACE inhibitors undergoing plasma exchange or plasma treatment
Removal of highly protein-bound drugs or immunoglobulins (with frequent plasma exchanges)

ACE, angiotensin-converting enzyme.

or gastrointestinal cramps, perioral numbness, distal paresthesias, and chest tightness. In sedated or unconscious patients, severe citrate toxicity may manifest as tetany, muscle spasm including laryngospasm, a prolonged QTc interval and decreased myocardial contractility [23]. Hypomagnesemia and hypokalemia may also occur, as the kidneys increase cation excretion into the urine to facilitate excretion of the citrate load. Although rare, fatal arrhythmias have occurred during therapeutic apheresis. To avoid these complications, ionized calcium should be monitored and intravenous calcium infused, as indicated, either through the return line or as an additive with the albumin replacement fluid.

Hypotension or vasovagal reactions occur in roughly 0.5% to 2.9% of therapeutic apheresis procedures [23,24]. Patients with preexisting hemodynamic instability or diminished vascular tone, as seen in certain neurologic disorders, may be at particular risk. In such patients, a net negative end fluid balance must be avoided. Transfusion reactions may occur if blood components are part of the replacement fluid. Allergic reactions have also been reported in some patients receiving albumin as the replacement fluid.

Hemostatic alterations and bleeding may occur in severely ill patients with baseline coagulopathy and/or severe thrombocytopenia. A typical 1.3-volume plasma exchange using albumin depletes most coagulation factors to approximately 25% to 45% of their preprocedure values [25]. Repletion time of these coagulation factors depends on their respective rates of synthesis, with most factors returning to baseline values by 24 hours. The exception is fibrinogen, which takes about 3 days to return to baseline values. Because fibrinogen levels are the most severely affected during the course of a series of plasma exchanges, preprocedure fibrinogen levels should be monitored, especially if the replacement fluid does not include at least 50% plasma. Therapeutic leukapheresis removes a portion of circulating platelets, and this decrement could be clinically significant in a patient with preprocedure severe thrombocytopenia. The postprocedure platelet count and coagulation status should be monitored in a critically ill patient, particularly if an invasive procedure is needed shortly after apheresis.

In some patients undergoing plasma exchange with albumin as the replacement fluid, a severe reaction consisting of flushing, hypotension, bradycardia, and dyspnea has been linked to concomitant use of angiotensin-converting enzyme (ACE) inhibitors [26]. This reaction is mediated by bradykinin, which is thought to be generated by prekallikrein-activating factor in the albumin preparation. These reports have led to the recommendation that ACE inhibitors be withheld for 24 to 48 hours (depending on the half-life of the specific drug) before plasma exchange using albumin [26]. If an emergency exchange is required in a patient on an ACE inhibitor, FFP should be used as the replacement fluid to avoid this reaction. Similar reactions involving ACE inhibitors have been seen in patients undergoing plasma treatment with specialized columns; thus, similar precautions must be followed [27].

An additional potential adverse effect of repeated plasma exchange is the removal of highly protein-bound therapeutic drugs and plasma immunoglobulins. The exact effects of exchange on individual drug levels have not been delineated. To avoid this complication, medications should be administered following a plasma exchange procedure whenever possible. Immunoglobulin levels should also be measured periodically in immunosuppressed patients undergoing a series of plasma exchanges, as these proteins will be nonselectively depleted from the circulation, and severe hypogammaglobulinemia could further predispose the patient to infections [28].

INDICATIONS IN CRITICAL CARE

Evidence-based guidelines for clinical applications are published by the American Society for Apheresis (ASFA) every few years [29]. Medical conditions are placed into categories from I to IV, with I indicating that therapeutic apheresis is known to be an effective primary or adjunct therapy based on randomized controlled clinical trials or broad noncontroversial experience, and category IV indicating no demonstrated efficacy, and possibly even a negative impact of therapeutic apheresis for the condition. Examples of evidence-based indications for therapeutic apheresis are shown in Table 113.3.

Therapeutic Plasma Exchange

In the intensive care unit, TPE is likely to be the most frequent apheresis procedure used. Antibody-mediated conditions known to respond to plasma exchange include idiopathic thrombotic thrombocytopenic purpura [16,30,31]; demyelinating diseases including acute inflammatory demyelinating polyneuropathy/Guillain–Barré syndrome [32–34]; severe, acute idiopathic inflammatory demyelinating diseases (Table 113.4); myasthenic crisis [43,44]; demyelinating polyneuropathy with IgG and IgA [45,46]; antiglomerular basement membrane (Goodpasture's) disease; and pulmonary hemorrhage associated with other forms of rapidly progressive glomerulonephritis (RPGN) [47,48]. Among patients with RPGN, the evidence supporting a potential benefit of plasma exchange derives from retrospective and case-control studies among more severely affected patients [49,50], whereas randomized controlled trials have yielded supportive results in some studies [38] but not others [39,40] (see Table 113.4). For patients with renal vasculitis due to causes other than anti-GBM disease, a review of randomized controlled clinical trials demonstrated a significant reduction in end-stage renal disease with use of TPE [41].

With the muscle-specific receptor tyrosine kinase antibody (MuSK-Ab) form of myasthenia gravis, TPE appears to be a more effective therapy than intravenous immunoglobulin (IVIg) infusion [51]. By comparison, with the acetyl cholinesterase receptor (AChR-Ab) form of myasthenia gravis, and with Guillain–Barré syndrome, plasma exchange is effective but not superior to or as tolerable as IVIg infusion [33,34,41] (see Table 113.4). For patients with acute attacks of demyelination, plasma exchange may be useful. Although there is only one randomized controlled trial [37], observations from this study and retrospective data indicate that at least 50% of patients with neuromyelitis optica (NMO), characterized by spinal and visual involvement, achieve increased function with plasma exchange, and that patients with steroid-refractory optic neuritis may also achieve some benefit [52]. A potential

TABLE 113.3

EVIDENCE-BASED INDICATION CATEGORIES FOR THERAPEUTIC APHERESIS FOR DISORDERS POTENTIALLY AFFECTING CRITICALLY ILL PATIENTS

Disease	Apheresis procedure	Indication	Recommendation
		Category	Grade
Renal			
Antiglomerular basement membrane antibody disease	Plasma exchange	I	1A
ANCA-associated rapidly progressive glomerulonephritis (dialysis dependence or diffuse alveolar hemorrhage [DAH])	Plasma exchange	I	1A 1C for DAH
Immune complex rapidly progressive glomerulonephritis	Plasma exchange	III	2B
Myeloma cast nephropathy	Plasma exchange	II	2B
Hemolytic uremic syndrome (typical, diarrhea associated)	Plasma exchange	IV	1C
Allograft rejection (antibody mediated)	Plasma exchange	I	IB
Autoimmune and rheumatologic			
Cryoglobulinemia (severe/symptomatic)	Plasma exchange	I	IB
Idiopathic thrombocytopenic purpura	Plasma exchange	IV	1C
Systemic lupus erythematosus cerebritis or DAH	Plasma exchange	II	2C
Systemic lupus erythematosus nephritis	Plasma exchange	IV	1B
Catastrophic antiphospholipid syndrome	Plasma exchange	II	2C
Hematologic			
Thrombotic thrombocytopenic purpura	Plasma exchange	I	1A
Hyperleukocytosis with leukostasis	Leukapheresis	I	1B
Sickle cell disease with acute stroke	Red cell exchange	I	1C
Sickle cell disease with acute chest syndrome	Red cell exchange	II	1C
Thrombocytosis (symptomatic, myeloproliferative origin)	Plateletpheresis	II	2C
Posttransfusion purpura	Plasma exchange	III	2C
Polycythemia vera or erythrocytosis	Erythrocytapheresis	III	2C
Hyperviscosity (monoclonal IgM, IgA, IgG)	Plasma exchange	I	1B
Coagulation factor inhibitors	Plasma exchange	IV	2C
Babesiosis (severe)	Red cell exchange	I	1B
Malaria (severe)	Red cell exchange	II	2B
Neurologic			
Acute inflammatory demyelinating polyradiculopathy (Guillain–Barré syndrome)	Plasma exchange	I	1A
Acute disseminated encephalomyelitis	Plasma exchange	II	2C
Chronic inflammatory demyelinating polyradiculopathy	Plasma exchange	I	1B
Myasthenia crisis	Plasma exchange	I	1A
Demyelinating polyneuropathy with IgG and IgA	Plasma exchange	I	1B
Demyelinating polyneuropathy with IgM	Plasma exchange	I	1C
Lambert-Eaton myasthenia syndrome	Plasma exchange	II	2C
Multiple sclerosis (acute, fulminant)	Plasma exchange	II	1B
Neuromyelitis optica	Plasma exchange	II	1C
Other disorders			
Drug overdose and poisoning	Plasma exchange	III	2C
Acute hepatic failure	Plasma exchange	III	2B
Toxic epidermal necrolysis	Plasma exchange	N/A	N/A
Severe sepsis and multiple-organ dysfunction syndrome	Plasma exchange	III	2B
Burn shock resuscitation	Plasma exchange	IV	2B

IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.
Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. *Category II*: Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. *Category III*: Disorders for which the optimum role of apheresis therapy is not established. Decision making should be individualized. *Category IV*: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. N/A indicates that the disorder is not ranked by the ASFA criteria.
Note: The Grade system has also been assigned in an effort to parallel an approach more commonly used to evaluate therapeutic recommendations.
Adapted from Guyatt G, Gutterman D, Baumann MH, et al: Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American college of chest physicians task force. *Chest* 129:174–181, 2006; also Adapted from evidence-based indications categorizations generated by the American Society for Apheresis (ASFA) Apheresis Applications Committee. Zbigniew M, Szczepiorkowski (eds): Clinical applications of therapeutic apheresis: an evidence based approach. 5th edition. *J Clin Apher* 25(3), 2010.

TABLE 113.4

RANDOMIZED CONTROLLED TRIALS AND SYSTEMATIC REVIEWS OF RANDOMIZED CONTROLLED TRIALS THAT UTILIZED THERAPEUTIC APHERESIS FOR DISORDERS IN CRITICAL CARE PATIENTS

Disease category [Ref.]	n	Intervention	Outcome
Severe sepsis and septic shock [35]	106	Plasma exchange (PE) vs. standard therapy	**28-d mortality** 18/54 (33%) PE 28/52 (54%) Control ($p = 0.05$)
Sepsis syndrome [36]	30	Plasma filtration (PF) vs. standard therapy	**14-d mortality** 8/14 (57%) PF 8/16 (50%) Control ($p = 0.73$)
Acute inflammatory demyelinating polyradiculopathy/Guillain–Barré syndrome (systematic review of six trials) [33]	649	PE vs. supportive care	**Mechanical ventilation at 4 wk** 85/315 (27%) Control 44/308 (14%) PE (RR 0.53; 95% CI 0.39–0.74, $p = 0.0001$) **Severe sequelae at 1 y** 55/328 (17%) Control 35/321 (11%) PE (RR 0.65; 95% CI 0.44–0.96, $p = 0.03$) **1-y mortality** 18/328 (5.5%) Control 15/321 (4.7%) PE (RR 0.85; 95% CI 0.42–1.45, $p = 0.70$)
Acute inflammatory demyelinating polyradiculopathy/Guillain–Barré syndrome (systematic review of five trials) [34]	582	PE vs. intravenous immunoglobulin (IVIg)	**Median time to discontinuation of mechanical ventilation (two studies)** 34 d ($n = 34$) PE vs. 27 d ($n = 29$) IVIg ($p =$ NS) 29 d ($n = 40$) PE vs. 26 d ($n = 44$) IVIg ($p =$ NS) **Mortality during follow-up** 9/286 (3.1%) PE 7/296 (2.4%) IVIg (RR 0.78; 95% CI 0.31–1.95, $p =$ NS)
Severe, acute idiopathic inflammatory demyelinating diseases of the central nervous system, including multiple sclerosis [37]	22	Active PE vs. sham PE (crossover allowed)	**≥ Moderate acute improvement** 8/19 (42%) Active PE therapy 1/17 (6%) Sham PE therapy
Rapidly progressive glomerulonephritis (RPGN), including antiglomerular basement membrane (anti-GBM) disease and antineutrophil cytoplasmic antibody (ANCA) associated disease [38]	44	PE vs. immunoadsorption (IA)	**6-mo median creatinine clearance** 49 mL/min PE 49 mL/min IA **6-mo mortality** 1/23 (4.3%) PE 2/21 (9.5%) IA ($p =$ NS)
RPGN, including anti-GBM disease and ANCA-associated disease [39]	33	PE vs. standard therapy with immunosuppression	**Dialysis-free survival among patients with type III RPGN** 42% PE ($n = 18$) 49% Control ($n = 15$; $p =$ NS)
RPGN, including anti-GBM disease and ANCA-associated disease [40]	32	PE vs. standard therapy with immunosuppression	**Patients on dialysis at study end** 3/16 (19%) PE 5/16 (31%) Control ($p =$ NS)
Renal vasculitis (adult) other than anti-GBM (systematic review of six trials) [41]		Use of PE	**3-mo response rate** Significant reduction in risk of end-stage renal disease ($p = 0.01$) **12-mo response rate** Significant reduction in risk of end-stage renal disease ($p = 0.002$)
Thrombotic thrombocytopenic purpura [16]	102	PE vs. plasma infusion (PI)	**6-mo response rate** 40/51 (78%) PE 25/51 (49%) PI ($p = 0.002$) **6-mo mortality** 11/51 (22%) PE 19/51 (37%) PI ($p = 0.036$)
Myasthenia gravis [42]	87	PE vs. intravenous immunoglobulin (IVIg)	**Day 15 variation of myasthenic muscular score** +18 PE ($n = 41$) +15.5 IVIg ($n = 46$; $p = 0.65$)

CI, confidence interval; *n*, number; NS, not significant; RR, relative risk; vs., versus.

mechanism of action of TPE with NMO is modulation of the serum autoantibody NMO-IgG, which has been implicated in disease pathophysiology [53].

The optimum role of TPE in the setting of severe sepsis and multiorgan dysfunction is not established. Two randomized controlled trials in adults using either continuous plasma filtration versus supportive care [36] or plasma exchange versus standard care [35] have been published. No differences were observed in the 14-day mortality rates of 14 patients with sepsis syndrome receiving 34 hours of continuous plasma filtration and 16 untreated control patients (57% vs. 50%) [36] (see Table 113.4). By comparison, the 28-day mortality rate was 33.3% among 54 patients with sepsis and septic shock treated with one or two TPE treatments compared with 53.8% among 52 nontreated control patients ($p = 0.05$) [35] (see Table 113.4). When differences between the control and experimental groups were considered using multiple logistic regression, the significance of the treatment variable on mortality was $p = 0.07$.

A nonrandomized observational cohort study evaluated hemodynamic and mortality outcomes in critically ill surgical patients with sepsis treated with TPE and continuous venovenous hemofiltration [54]. No overall difference in mortality was observed between treated patients and an untreated historical control group (42% vs. 46%); however, patients with organ failure limited to one or two systems appeared to benefit, with mortality rates of 10% among 10 treated patients versus 38% among 16 untreated control patients [54]. Although encouraging, these data must be supported by results from additional well-designed randomized controlled trials before plasma exchange can be recommended as a noninvestigational therapy for this indication [55].

Use of red blood cell exchange may be warranted for selected patients with sickle cell disease who are experiencing stroke, acute chest syndrome (ACS), priapism, or multiple organ failure as a complication of their disease [56]. Because automated red cell exchange (also called erythrocytapheresis) can more rapidly reduce the level of hemoglobin S-positive cells (to the goal of < 30%) while maintaining euvolemia and minimizing hyperviscosity complications, this modality has been utilized in preference to simple transfusion by many centers. Although this makes intuitive sense, the data needed to show a clear advantage of automated red cell exchange over simple transfusion are lacking. An observational, retrospective cohort analysis found no differences in postprocedure and total lengths of stay for patients with ACS treated with automated red cell exchange ($n = 20$) compared with those who received simple transfusion support ($n = 20$) [57]. Moreover, the apheresis group required, on average, four times as many units of donor red cells.

Manual exchange transfusion, in which phlebotomized blood is replaced by simple transfusions of allogeneic red cells and FFP, has the added theoretical advantage of reducing the levels of plasma inflammatory mediators, which might augment vaso-occlusive tissue injury in patients with ACS [58]. One nonrandomized trial used a combination of TPE and automated red cell exchange for 7 patients with severe ACS and multiorgan failure, and observed an 86% 1-year survival [59]. Despite these observations, the optimal approach for critically ill patients with ACS and other severe complications remains undefined, in part because crossmatch-compatible blood may be very difficult to locate for heavily transfused sickle cell patients with multiple alloantibodies. Adequately powered randomized clinical trials are sorely needed to clarify the indications for automated or manual red cell exchange versus simple transfusion support and the potential role of TPE.

Red cell exchange may also be useful in patients with severe clinical manifestations of falciparum malaria or babesiosis [60,61]. Although a meta-analysis performed in 2002 showed no survival benefit of red cell exchange compared with antimalarials and aggressive supportive care alone [62], many case reports and series suggest a benefit in clinical status with rapid reduction of hyperparasitemia using adjunctive manual or automated red cell exchange [61,63,64]. The Centers for Disease Control and Prevention (CDC) also recommends consideration of red cell exchange as adjunctive therapy if *Plasmodium falciparum* parasitemia is greater than 10%, or if the patient has severe malaria manifested by nonvolume overload pulmonary edema, renal complications, or cerebral malaria [65]. Quinidine administration should not be delayed and may be given concurrently with the exchange. As in fulminant malaria, several case reports demonstrate that patients with overwhelming parasitemia from Babesia also quickly respond to red cell exchange [61].

Automated red cell exchange may be considered as an alternative to large volume phlebotomy in selected patients with uncontrolled erythrocytosis and polycythemia vera with acute thromboembolism, severe microvascular complications, or bleeding [66]. This method can quickly and more safely normalize the hematocrit in patients who are hemodynamically unstable.

Leukapheresis

Leukapheresis (i.e., selective removal of white blood cells) is commonly used in patients with acute myeloid leukemia (AML) experiencing symptoms of intravascular leukostasis. Signs and symptoms typically manifest as neurologic alterations (confusion, mental status changes, altered level of consciousness) or pulmonary compromise (hypoxemia, diffuse lung infiltrates). Leukapheresis is indicated in patients with AML and a circulating blast count greater than 50,000 per µL who are clearly demonstrating signs of intravascular leukostasis (i.e., symptoms not attributable to infection, bleeding, or metabolic derangements) [67,68]. Leukapheresis may be warranted sooner in monocytic subtypes of AML, as signs of intravascular leukostasis may be seen at blast counts less than 50,000 per µL or after the start of chemotherapy. Prophylactic leukapheresis should be considered in AML patients with circulating blast counts greater than 100,000 per µL, particularly if the count is rapidly rising and definitive therapy with induction chemotherapy is delayed [refer to ASFA Guideline Ref]. In comparison with AML, leukostasis complications are rare in patients with acute lymphoblastic leukemia (ALL) and circulating blast counts less than 400,000 per µL. Studies have shown that prophylactic leukapheresis for asymptomatic patients with ALL and hyperleukocytosis does not offer additional benefit above aggressive supportive care and chemotherapy [69].

Plateletpheresis

Plateletpheresis should be considered as an urgent intervention in patients experiencing thrombosis or hemorrhage in the setting of uncontrolled thrombocytosis associated with a stem cell disorder [70]. Such stem cell disorders include essential thrombocythemia, polycythemia vera, idiopathic myelofibrosis, or unclassified myeloproliferative neoplasm. The goal of the plateletpheresis is to decrease the count below 1 million per µL, with a target closer to 500,000 per µL [70]. Plateletpheresis may also be indicated for the management of perioperative thrombohemorrhagic complications in patients with myeloproliferative neoplasms undergoing splenectomy [71].

For any apheresis procedure, consultation with the apheresis team can be useful in assessing experience and available data

for a given condition. The apheresis physician and team should be viewed as partners in determining the treatment plan. Initial discussion with the apheresis physician will include whether the indication is urgent or routine, the impact of apheresis on other treatment modalities, volume management, fluid replacement, and vascular access. Ongoing discussions should continue through the patient's course so that appropriate adjustments can be made to optimize the therapy.

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CHAPTER 114 ■ TRANSFUSION THERAPY: BLOOD COMPONENTS AND TRANSFUSION COMPLICATIONS

TERRY GERNSHEIMER

Transfusion support can be a key element in decreasing morbidity and mortality of the critically ill patient by the support of oxygen delivery and correction of hemostatic abnormalities. An understanding of the benefits, limitations, and risks of blood component therapy is of fundamental importance in the intensive care setting. This chapter will outline blood components available for transfusion, their appropriate dosages, and therapeutic effects. Complications of transfusion therapy, including infectious risks, transfusion reactions, effects of storage, and immunomodulatory effects, as well as methods to minimize these complications, will be discussed.

BLOOD COMPONENT THERAPY

Cellular Blood Components

Red Blood Cells

One unit of "packed" red blood cells (pRBC) is processed by the removal of platelet rich plasma from a donated unit of whole blood and contains approximately 200 mL red blood cells, usually less than 50 mL plasma, and an additive that brings the component to 300 to 350 mL in total volume. Depending upon the additive, the storage life at 4°C will be from 35 to 42 days. Red blood cell storage has multiple theoretic and measurable effects. Any platelets still present in the component are rendered inactive by the cold storage. As red blood cells are stored, intracellular potassium leaks into the plasma space. 2,3-Diphosphoglyceric acid (2,3-DPG) may also be depleted from the red blood cells, which theoretically could cause increased oxygen affinity and decreased release of oxygen at the tissues [1]. This effect reverses after several hours in vivo but may be clinically significant in the patient undergoing massive transfusion. Stored pRBC also have elevated plasma ammonia levels, elevated PCO_2, lowered pH, and increased amounts of microaggregates. These all have theoretic effects on oxygen delivery when given rapidly in large amounts. Massive transfusion can also theoretically result in hypocalcemia and hyperkalemia.

In 1993, Marik and Sibald [2] reported the incidental finding of increased gastric pH in 23 patients with septic shock transfused with 3 units of pRBC, but Walsh failed to find a similar effect in a small randomized control trial in 22 patients with septic shock transfused with pRBC stored for less than 5 or more than 20 days [3]. Hébert found a higher incidence of mortality and life-threatening complications who received blood stored less than 8 days when compared with standard therapy in a randomized study of 66 patients undergoing cardiac surgery [4]. Although van der Watering did find longer ICU stays and decreased survival in a retrospective study of 2,732 patients undergoing coronary artery bypass graft (CABG) who received blood that had undergone a median age of ≥ 18 days or more versus less than 18 days of storage, this difference was not apparent in a multivariate analysis [5]. A retrospective report of a large number of patients (5,902) by Koch et al. [6] showed a significant increase in mortality and complications at 1 year in patients undergoing CABG who received blood > 14 days of age versus < 15 days of age, but differences in characteristics of the two patient groups complicated the analysis. The effect of storage age remains controversial [7] and will require careful

prospective randomized clinical trials in adequate numbers of patients before the true clinical significance of storage age and the nature of the effect becomes clear [8].

Other than factors V and VIII, the activity of most coagulation factors are quite stable during storage, even after 2 weeks, and therefore whole blood (without the plasma removed), when available, may be used in selected patients with coagulopathy and bleeding, and can reduce donor exposure by limiting administration of multiple products (e.g., red cells and plasma) [9]. Factor V levels in stored whole blood are well above 50% and therefore adequate for hemostasis. Factor VIII is produced by endothelial cells as well as by the liver, and levels increase in the setting of inflammation, so a decrease with storage may be less clinically relevant. Whole blood may also be the preferred form of red cell transfusion in patients who require intravascular volume expansion as well as increased oxygen carrying capacity.

The primary function of hemoglobin in RBCs is to transport oxygen efficiently from the lungs to the various tissues of the body. Oxygen transport is a complex process regulated by several different mechanisms of control, involving the heart and vascular system. The most important functional feature of the hemoglobin molecule is its ability to combine loosely and reversibly with oxygen. Decreased hemoglobin oxygen affinity and increased tissue oxygen delivery occur with increased temperature and decreased pH, when there are increased tissue requirements. Oxygen is also less tightly bound with increased 2,3-DPG levels, which increases in the chronically ill patient [10]. In the seriously ill patient with severe acidosis and septic shock, however, 2,3-DPG levels may decrease resulting in decreased tissue oxygen delivery.

In a normovolemic, otherwise healthy individual, the effect of a decreased hematocrit is decreased blood viscosity and a compensatory augmentation of cardiac output and blood flow to most organs [11]. Human and animal studies reveal remarkable tolerance for hematocrit levels as low as 15% [12,13], but an optimum value has not been well defined and is very dependent on the patient's physiologic state. A decrease in the hematocrit also involves a redistribution of blood flow away from the endocardium and may have adverse effects on ischemic cardiac tissue. A retrospective analysis of patients older than 65 years hospitalized with acute myocardial infarction found that in patients with a hematocrit less than 30.0% (and perhaps $<33.0\%$) on admission, transfusion was associated with a lower 30-day mortality rate [14]. However, in patients who had undergone elective CABG, postoperative transfusion for hemoglobin levels greater than 8 did not improve morbidity, mortality, or complication rates [15]. Postoperative patients with known vascular disease and hematocrits less than 28% have been shown to have a significant increase in myocardial ischemia and morbid cardiac events [16], and in one study that retrospectively evaluated patients refusing transfusion on religious grounds, low preoperative hemoglobin was associated with increased morbidity and mortality in patients with cardiovascular disease undergoing surgery [17]. In a large multicenter, randomized trial, there was no difference in adverse outcomes when patients with cardiac disease were transfused at a hemoglobin threshold of 7.0 g versus 10 g [18]. In this study of more than 800 patients, less acutely ill, younger patients (<55 years of age) without cardiac disease who were randomized to the more liberal (higher) transfusion trigger had an overall higher mortality rate. A restrictive RBC transfusion strategy also did not adversely affect outcomes related to mechanical ventilation [19]. In postoperative patients without cardiovascular disease, few data support interference with wound healing or increased anesthesia risk at hemoglobin levels of less than 10 g per dL [20], and hemoglobin values as low as 7 g per dL appear to be safe in otherwise healthy individuals [21].

Advocates of restrictive transfusion strategies point out that transfusing to normal hemoglobin concentrations does not improve organ failure and mortality in the critically ill patient [22] and to data that transfusion may actually be associated with increased infection rates, morbidity and mortality [23]. Proponents of more liberal transfusion strategies point out the possible detrimental effects that may be associated with oxygen debt [24]. A thoughtful transfusion policy is dependent on the time the anemia developed over and can be expected to continue; additional medical problems that may make a patient more susceptible to anemia, such as tissue ischemia and pulmonary disease; and whether there is rapid, ongoing blood loss.

Blunted erythropoietin responses have been noted in critically ill pediatric [25] and adult patients [26]. Long-term intensive care patients may not only fail to increase their erythropoietin level in response to anemia but may have correctable nutritional deficiencies and iron profiles consistent with anemia of chronic disease. Although erythropoietin therapy increases red blood cell production and appears to decrease transfusion needs [27–29], the effect can take weeks and may reduce blood cell transfusion only minimally. It is an expensive alternative to more restrictive transfusion strategies to reduce transfusion exposure in appropriately chosen patients.

Studies in animal models [30] and in humans [31,32] reveal that platelet function and interaction with subendothelium decline at lower hematocrits. In the thrombocytopenic and thrombocytopathic (e.g., uremic) patient, transfusion to higher hematocrit values is appropriate in the patient at risk of bleeding.

Therapeutic Effect. The response to red cell transfusion will depend on intravascular volume, but it can be estimated that one unit of pRBC will increase the hematocrit by approximately 3%. It may take up to 24 hours while intravascular volume equilibrates for full effect. Rapid ongoing red cell destruction or splenic sequestration may also affect the hematocrit increment as well as the red cell survival.

Emergency Blood Usage. Uncrossmatched type O RBCs can be used for a bleeding patient in dire emergency. Type O, Rh-negative RBCs can be transfused to people of any blood type with only a slight risk of hemolysis. This risk increases in patients who have previously been transfused or pregnant and may have formed antibodies [33]. Type O, Rh-positive RBCs are sometimes used for women who are beyond childbearing age and in adult males. When Rh-positive RBCs are used in an Rh-negative patient, there is a chance of a D immunization, and if the patient requires emergency transfusion in the future, they may have preformed antibodies. Anti-D antibodies do not generally cause immediately intravascular hemolysis but rather a slow extravascular hemolysis, so the risk is small overall. Anti–Rh-D (Rhogam®) may be given within 48 hours of giving transfusion of Rh-positive blood to an Rh-negative woman of childbearing age, but the amounts required limit its use in prevention of immunization.

Platelets

Platelets are essential for the initial phase of hemostasis. Following exposure of subendothelial substances, platelets adhere to the subendothelial tissues by von Willebrand factor and other adhesive proteins. This initial adhesion activates platelets, causing release of platelet alpha and dense granules. Some of these granule contents, including factor V, fibrinogen, von Willebrand factor, and calcium, move to the extracellular space via the open canalicular system, increasing their concentrations in the immediate "neighborhood" of the platelet. With platelet activation, anionic phospholipids move to the platelet surface, forming binding sites collectively known as platelet factor 3, upon which coagulation factors can interact with

calcium to form IXa, Xa, and thrombin. Platelet glycoprotein IIb-IIIa is exposed and binds fibrinogen. Thrombin generation causes further platelet activation and converts fibrinogen to fibrin, resulting in a platelet-fibrin mass that can effectively cease bleeding from a break in the endothelium. Fifteen percent of the platelet's protein is actin and myosin, which, upon coupling in the presence of increased concentrations of adenosine diphosphate (ADP) and calcium, leads to cytoskeletal movement and clot retraction.

The threshold of thrombocytopenia at which bleeding may occur will vary depending on the patient's clinical condition. In general, spontaneous bleeding does not occur until the platelet count falls below 5,000 to 10,000/μL [34–37]. The recommended "trigger" for prophylactic platelet transfusions in patients undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) without bleeding or other comorbid conditions is less than 10,000/μL. For the majority of invasive procedures, a platelet count of 30 to 50,000/μL will be adequate. For high-risk procedures, such as neurologic or ophthalmologic surgeries, a platelet count of 100,000/μL is recommended by the American Society of Anesthesiology [38] and the College of American Pathologists [39]. Technique and experience appear to be as least as important predictors of bleeding following placement of catheters as clotting abnormalities, even in patients with isolated platelet counts less than 20,000/μL [40]. The risk of bleeding with thrombocytopenia increases when complicated by other hemostatic abnormalities.

Platelet counts less than 50,000/μL are associated with increased risk of microvascular bleeding in the massively transfused patient [41]. For this reason, platelet transfusion has been advocated with replacement of every blood volume to avoid the effect of dilutional thrombocytopenia [42]; however, some investigators have found that patients receiving prophylactic platelet transfusion were no less likely to develop microvascular bleeding [43]. In patients with brisk ongoing blood loss, rapid turnaround of platelet counts can direct diagnosis and are important in managing transfusion therapy.

Higher transfusion triggers may be indicated with abnormal platelet function [44]. Platelet function abnormalities may be congenital or acquired. Medications, sepsis, malignancy, tissue trauma, obstetrical complications, and extra corporeal circulation may all adversely affect platelet function. Liver and kidney disease may be associated with severe thrombocytopathy. Hypothermia prolongs bleeding time in trauma patients [45] and arterial hemorrhage in animals [46]. Glycoprotein IIb-IIIa inhibitors may affect platelet number as well as function. If platelet dysfunction is present, the patient with a disrupted vascular system (e.g., trauma or surgery) will require a higher platelet count to achieve hemostasis. Higher counts may be necessary to prevent spontaneous bleeding as well. The transfused platelets may quickly become dysfunctional in the patient, and other therapy may be necessary, such as dialysis and dialysis and desmopressin acetate (DDAVP) for bleeding in renal failure, rewarming of the hypothermic patient, or correction of acidosis.

In several situations, platelet transfusions may not be indicated unless there is significant bleeding. In autoimmune thrombocytopenias (e.g., immune thrombocytopenia (ITP) and posttransfusion purpura), transfusion increments are usually poor and platelet survival is short. Administration of intravenous immune globulin in high doses may improve transfusion response and survival as well as treat the underlying disease [47]. There have been reports of rapid exacerbation of the thrombotic process in the cerebrovascular circulation in patients with thrombotic thrombocytopenic purpura (TTP) following platelet transfusion [48]. These reports are anecdotal and may represent disease progression, but in general, platelet transfusions are felt to be relatively contraindicated in TTP unless there is clinically significant bleeding.

TABLE 114.1

EXPECTED PLATELET INCREMENT WITH TRANSFUSION[a]

	1 unit[b]	4 units	6 units
	0.8×10^{11}	3.2×10^{11}	4.8×10^{11}
50 lb/23 kg	17,600/μL	70,400/μL	105,600/μL
100 lb/45 kg	8,800	35,200	52,800
150 lb/68 kg	5,900	23,500	35,200
200 lb/91 kg	4,400	17,600	26,400

[a] In a patient with a normal sized spleen and without platelet antibodies.
[b] Whole blood platelets. An apheresis platelet component contains the equivalent of 4–8 units of whole blood platelets.

Pooled random donor platelet concentrates are prepared from platelets that have been harvested by centrifuging units of donated whole blood. Up to 8 units of platelets, each from a separate donor, can be pooled into a single bag for transfusion. All units are from the same ABO type. If ABO compatible platelets are unavailable, in most cases, pooled ABO incompatible platelets can be substituted with very little risk. The usual adult dose is 1 unit per 15 kg of body weight. Four to six units of pooled random donor platelets are frequently used in patients receiving prophylactic transfusions; however, a study of more than 1,200 hospitalized patients with thrombocytopenia due to chemotherapy or HSCT for hematologic malignancy showed no difference in bleeding incidence and decreased platelet exposure overall when transfused with low ($1.1 \times 10^{11}/m^2$), medium ($2.2 \times 10^{11}/m^2$), or high ($4.4 \times 10^{11}/m^2$) doses of platelets prophylactically for platelet counts of less than 10,000/μL [49], suggesting that a dose of only 3 or 4 units of pooled random donor platelets is adequate. Patients who received smaller doses did require more frequent transfusions, making this strategy less appropriate for outpatient transfusion.

In a 70-kg patient with a normal sized spleen, each unit is expected to increase the platelet count by approximately 7,000/μL (Table 114.1) when checked 10 minutes to 1 hour after transfusion [50]. The survival of transfused platelets averages 3 to 5 days but will decrease if a consumptive process is present. Platelet concentrates also contain about 60 mL of plasma per unit and small numbers of red blood cells and leukocytes. Platelet units must be maintained at room temperature, as platelets lose shape and release their granular contents when refrigerated. Apheresis platelets, collected from a single donor, are prepared in components equivalent to 4 to 6 pooled units. An apheresis platelet concentrate contains 200 to 400 mL of plasma and, if the plasma is of an incompatible type, may be reduced in volume by centrifugation, although this results in an approximate 10% to 15% loss of platelets and probably some loss of function. Apheresis platelets may be collected for a specific recipient from a family member or other human leukocyte antigen (HLA) compatible donor for patients that have become refractory to random donor platelet transfusions due to alloimmunization. Leukocyte reduction of transfused cellular blood components has been clearly shown to reduce the rate of alloimmunization in patients undergoing chemotherapy for acute myelocytic leukemia [51].

Granulocytes

The degree of granulocytopenia is directly related to the risk of infection [52]. Although antibiotics have improved morbidity and mortality in patients affected by prolonged periods of

neutropenia, most antimicrobials are less effective in the presence of granulocytopenia. Bacterial and, more particularly fungal, infections remain a major cause of death in HSCT patients despite shortening of the period of neutropenia with hematopoietic growth factors [53]. Granulocytes collected by continuous flow centrifugation and filtration leukapheresis function normally in vitro in the quantitative nitroblue tetrazolium, oxygen consumption, and chemotaxis assays [54]. Bacterial killing by filtration leukapheresis granulocytes, which circulate for several hours posttransfusion, is only slightly decreased compared with granulocytes collected by continuous flow centrifugation. Transfused granulocytes rapidly migrate to sites of infection [55].

Early studies showed promise for the use of granulocyte transfusion for treatment of documented infections in neutropenic patients [56–58]; however, their usefulness in the prevention of infection has been more controversial [59], due to limitations in the inability to collect cells in sufficient amounts to provide an effective transfusion dose, poor response to granulocytes in heavily transfused, alloimmunized patients [60], and the early development of alloimmunization in patients transfused with granulocytes [61]. To this end, HLA-compatible donors have been administered corticosteroids prior to granulocyte collection with some limited success.

The administration of granulocyte colony-stimulating factor has been shown to be safe when given to normal donors [62] and has been administered to donors prior to collection to increase collection and posttransfusion increments [63,64]. Whether this will increase the efficacy of granulocyte transfusion in treatment of infection will require further study.

Plasma Components

Fresh Frozen Plasma

One unit of fresh frozen plasma (FFP) is the plasma taken from a unit of whole blood. It is frozen within 8 hours of collection and contains all coagulation factors in normal concentrations. It is free of red blood cells, leukocytes, and platelets. Plasma may also be provided as "frozen plasma" or "thawed plasma." These components are prepared by methods similar to plasma, and their factor concentrations differ only slightly. All will be considered here collectively as "FFP." One unit contains approximately 200 to 250 mL and must be ABO compatible (type AB is the universal donor type). Rh factor need not be considered. Since there are no viable leukocytes, FFP carries minimal risk of cytomegalovirus (CMV) transmission or graft versus host disease (GVHD).

FFP transfusion is indicated in patients with documented coagulation factor deficiencies and active bleeding. FFP should not be used to correct isolated deficiencies in clotting factors when a concentrated replacement source, such as factor VIII or IX, is available, as these concentrates are either recombinant or have undergone processing to inactivate viruses and can correct the deficiency using a much smaller infused volume. Factor deficiencies may be congenital or acquired secondary to liver disease, warfarin anticoagulation, disseminated intravascular coagulation (DIC), or massive replacement with red blood cells and crystalloid/colloid solutions. Usually, there is an increase of at least 1.6 times the normal prothrombin time (PT) or activated partial thromboplastin time (aPTT) before clinically important factor deficiency exists. This corresponds to levels of most factors less than 20% of normal. Above these levels, most routine non–major invasive procedures such as line placement [27], liver biopsy [65], and thoracentesis [66] are not associated with an increased risk of bleeding complications; however, the acceptable upper limits of PT and PTT prior to invasive procedures have not been evaluated in a large prospective randomized study to date [67–69].

TABLE 114.2

FRESH FROZEN PLASMA (FFP)—DOSAGE FOR TRANSFUSION

Volume of 1 unit FFP: 200–250 mL 1 mL plasma contains 1 unit coagulation factors **1 Unit FFP contains 220 units coagulation factors** Factor recovery with transfusion = 40% **1 Unit FFP provides ≈80 units coagulation factors** 70 kg × 0.05 = plasma volume of 35 dL (3.5 L) $\frac{80 \text{ unit}}{35 \text{ dL}}$ = 2.3 unit/dL = 2.3% (of normal 100 unit/dL)
In a 70-kg patient: **1 Unit FFP increases most factors ≈2.5%** **4 Units FFP increase most factors ≈10%**

In the massively transfused patient, consumption and dilution of coagulation factors may cause rapid development of coagulopathy. Patients with a PT or aPTT ratio (reference midrange normal value divided by actual) 1.8 or more had an 80% to 85% chance of exhibiting microvascular bleeding, and either of these tests should be closely monitored during resuscitation of the bleeding patient [33]. FFP transfusion is indicated when the ratio exceeds 1.5 times the midrange normal value in these patients [30]. Usually an increase in factor levels of at least 10% will be needed for any significant change in coagulation status, so the usual dose is 3 to 4 units (approximately 10 to 15 mL per kg), but the amount will vary depending on the patient's size and clotting factor levels (Table 114.2). Reversal of warfarin anticoagulation is indicated only if significant bleeding or risk of bleeding is present. FFP may be used for this purpose, but often, recurrent transfusion is required to maintain normal factor levels.

FFP is indicated in the treatment of TTP, most commonly in conjunction with plasmapheresis. Many other disorders are treated by plasmapheresis, but usually FFP replacement is not used. FFP should *not* be used for volume expansion unless the patient also has a significant coagulopathy and is bleeding.

Cryoprecipitate

Cryoprecipitate is prepared from plasma and contains fibrinogen, von Willebrand factor, factor VIII, factor XIII, and fibronectin. Cryoprecipitate is supplied in bags (each made from one whole blood unit) from multiple donors that have been resuspended in saline or plasma and pooled prior to transfusion. It must be kept at room temperature. The concentration of fibrinogen in cryoprecipitate units is up to 10 times that in FFP and therefore blood levels can be increased rapidly with much smaller volumes.

Fibrinogen levels can drop rapidly in DIC and is usually associated with other coagulation abnormalities that may in combination be treated with FFP. Isolated hypofibrinogenemia is infrequently associated with bleeding in adults, and correction should be reserved for patients with clinical bleeding or patients who are a risk of bleeding due to imminent invasive procedures or trauma [26] with significant hypofibrinogenemia (< 100 mg per dL).

Cryoprecipitate should not be used for patients with von Willebrand disease or hemophilia A (factor VIII deficiency) unless they do not (or are not known to) respond to DDAVP, and recombinant and/or virally inactivated preparations are not available. It is usually given for factor XIII deficiency, when virus-inactivated concentrates of this protein are not available.

Cryoprecipitate is sometimes useful if platelet dysfunction associated with renal failure does not respond to dialysis or DDAVP and in other platelet function defects [70].

The amount of fibrinogen per bag of cryoprecipitate can vary widely between blood centers depending on the donor's fibrinogen concentration. The approximate fibrinogen increment with each bag of cryoprecipitate transfused can be calculated by the formula: 25 mg/plasma volume (in liters). Six bags will increase the fibrinogen level of a 70-kg patient approximately 45 mg per dL. To replace factor VIII or von Willebrand factor when specific factor concentrates are unavailable, the usual dose is 1 bag per 10 kg of body weight. Approximately 150 units of factor VIII and von Willebrand factor are provided per bag. Although single units of cryoprecipitate can be used in the preparation of locally applied fibrin glue for surgery, commercially available, virally inactivated concentrates have a higher fibrinogen concentration and are preferred for this purpose. A patient may donate autologous plasma for processing into cryoprecipitate prior to a planned surgical procedure.

Human fibrinogen concentrate (RiaSTAP®) is a heat-treated, lyophilized fibrinogen (coagulation factor I) powder made from pooled human plasma. It is indicated for bleeding or procedure prophylaxis in patients with congenital hypofibrinogenemia or dysfibrinogenemia.

COMPLICATIONS OF TRANSFUSION

Transfusion-Related Risks

Infectious Complications

Since the recognition that human immunodeficiency virus (HIV) could be transmitted by blood transfusion in the mid-1980s, exclusion of donors with high risk has done more to decrease transfusion transmitted infection than any testing that has been implemented since that time [71]. Enzyme-linked immunosorbent assay (ELISA) testing for anti-HIV antibody was instituted in 1985 dropping the risk of HIV transmitted infection to 1 in 667,000 units [72]. The addition of P24 antigen decreased the window period between infection and detection to approximately 16 days [73].

Blood centers began clinical trials in April 1999 to screen blood with a polymerase chain reaction (PCR) test for hepatitis C virus (HCV) and HIV RNA. Although confirmed data are not available, the current estimated risks/unit are as low as 1:2,000,000 for HIV and HCV [74]. Risks for other viral transmissions are estimated to be 1:500,000–750,000 for hepatitis B and 1:3,000,000 for human T-lymphotropic virus I and II [75,76].

CMV is a DNA virus acquired as a primary infection with body secretions, blood products, or organ allografts. Infection in a normal host usually is asymptomatic but remains latent for life and can cause recurrent infection when it reactivates. CMV infection and seropositivity are extremely common, being 40% in highly industrialized areas, and is close to 100% in warmer climates, densely populated areas, and developing countries [77]. Transfusion-associated CMV infection in the immunocompetent patient with a normal immune system is usually asymptomatic, occurring 4 to 12 weeks after blood component exposure in 0.9% to 17% of patients [78]. In CMV-negative, immunosuppressed neonates and transplant and HIV-positive patients, the risk of CMV infection leading to severe end-organ disease and organ allograft rejection is high [79]. Leukocyte depletion of blood is equivalent to CMV seronegative blood in preventing CMV infection through transfusion [80] but may be more expensive and indicated only if CMV-negative blood is not available or leukocyte-depleted blood components are being provided for another reason. Although CMV seronegative blood is transfused to organ transplant recipients in some centers to prevent infection with secondary strains, the clinical relevance of this practice has not been demonstrated.

Bacterial contamination of red blood cell and platelet units may occur during collection. Red blood cell units may be contaminated with cold-loving organisms such as Yersinia. Platelets are stored at room temperature and multiple organisms can grow in those conditions. Although staphylococcus and streptococcus are most frequently implicated, Gram-negative organisms have also been identified [81]. The incidence of bacterial contamination of platelets has been estimated to be as high as 0.1% [82]. The institution of bacterial testing of platelets in 2004 in the United States is expected to decrease this risk [83]. Symptoms of hypotension, fever, and chills almost always occur within 3 hours of the transfusion and may be complicated by severe shock and DIC [84]. Both the patient and the blood component bag should be cultured if bacterial contamination is suspected.

Other organisms that can be transmitted by blood transfusion include other hepatitis viruses, malaria, and, rarely, syphilis. Trypanosoma cruzi, the parasite responsible for Chagas disease is becoming a commonly transfusion transmitted disease in Central and South America and has been reported in some Southern Border states. Fear of transfusion transmission of new variant Creutzfeldt-Jakob disease has led to stringent criteria on blood donor eligibility and institution of universal leukoreduction in some European countries, but the risk of infection by transfusion is low [85] and testing is not universal.

Transfusion Reactions

A transfusion should be stopped immediately whenever a transfusion reaction is suspected.

An **acute hemolytic transfusion reaction** (AHTR) occurs following transfusion of an incompatible blood component. Most are due to naturally occurring antibodies in the ABO antigen system, but AHTR may occur with incompatibility of Rh, Kell, Kidd, Lewis, and other red blood cell antigen systems. The vast majority of cases are due to failure of appropriate systems to identify the correct transfusion recipient [86]. Signs and symptoms include fever, hypotension, tachycardia, dyspnea, chest or back pain, flushing, and severe anxiety. Release of cytokines, such as tumor necrosis factor, interleukin 8, and monocyte chemoattractant protein-1 [87], is followed by fever, capillary leak, and activation of the hemostatic mechanism. If the reaction is severe, it may go on to cause a consumptive coagulopathy (DIC) and renal failure due to shock and deposition of thrombi in arterioles. Hemoglobinuria may be the first sign of hemolysis in the sedated patient. Centrifuging a tube of blood and examining the plasma for a reddish discoloration can quickly make the diagnosis. Treatment should first of all be immediate discontinuation of the transfusion as soon as AHTR is suspected and maintenance of venous access and fluid resuscitation if necessary. Pressor support may be necessary along with central venous pressure or Swann Ganz monitoring. AHTR is rare, estimated at 1:77,000 units [88].

Delayed hemolytic transfusion reactions (DHTRs) usually occur in patients who have been previously sensitized to an antigen through transfusion or pregnancy. A fall in titer over time may make incompatibility undetectable. A subsequent transfusion causes recall of the antibody followed by a falling hematocrit 5 to 10 days later. The hematocrit will continue to fall until all of the incompatible transfused cells have been destroyed. DHTR can result in symptomatic or asymptomatic hemolysis but has only rarely been reported to cause severe

morbidity or mortality [89]. Once recognized, the patient is usually easily supported by transfusion of compatible red blood cells.

Febrile nonhemolytic transfusion reaction (FNHTR) is a 1°C rise in temperature or greater that cannot be explained by the patient's clinical condition. FNHTR usually occurs within 1 hour of completion of the transfusion. Reactions are more common with platelet transfusions and in patients who have been heavily transfused and can be quite severe. FNHTR is often due to sensitization to antigens on donor leukocytes [90]. Cytokines, released from the white cells during storage of cellular blood components, also appear to play a role [91]. Prestorage leukocyte depletion of red blood cells and platelets by filtration may be helpful in patients for whom this is a problem. Leukocyte-reduced single-donor apheresis platelets are a possible alternative to leukocyte depletion by filtration of pooled random donor platelets. Occasionally, patients with persistent febrile reactions will require removal of most of the plasma (volume reduction) from platelet preparations. FNHTR should be differentiated from bacterial contamination, which is usually associated with higher fevers and other symptoms of sepsis. Antipyretics can be used to prevent or treat FNHTR. Meperidine may be useful in the treatment of rigors.

Transfusion-related acute lung injury (TRALI) can be indistinguishable from adult respiratory distress syndrome [92,93], involving severe bilateral pulmonary edema and hypoxemia. Symptoms of dyspnea, hypotension, and fever typically begin 30 minutes to 6 hours after transfusion and the chest x-ray shows diffuse nonspecific infiltrates. Ventilatory support may be required for several days before resolution but approximately 80% of patients improve within 48 to 96 hours. TRALI occurs when donor plasma contains an antibody, usually against the patient's HLA or leukocyte specific antigens. Lipids generated during prior storage of the transfused product and preexisting lung damage also appear to play parts in the pathogenesis of TRALI. Less often, the patient may have antibodies against donor leukocytes in the component. The blood center should be notified promptly so that components from the donor can be quarantined and the donor tested for antibodies against the patient.

Transfusion-associated cardiovascular overload (TACO) may occur in patients sensitive to increased amounts of intravascular volume with transfusion and may initially present a clinical picture similar to TRALI. Unlike TRALI, diuresis is usually effective in its treatment.

Allergic and anaphylactic reactions are common and are usually due to preformed immunoglobulin E antibodies to specific proteins in the donor's plasma. Mild urticaria complicates up to 3% of plasma infusions [94] and can be avoided with future transfusions by pretreatment with antihistamines, and in severe cases with corticosteroids. Only in cases of severe reactions (anaphylaxis), is washing of RBCs and platelets to remove all plasma indicated. Slowing of the rate of transfusion and centrifugation to remove some of the plasma in a platelet component will sometimes be effective in preventing future reactions in patients for whom this is a recurrent problem.

Transfusion-related graft versus host disease (TRGVHD) is due to infusion of donor lymphocytes that engraft and then proliferate in response to stimulation by foreign (host) antigens. TRGVHD typically begins 2 to 50 days after transfusion with rash, diarrhea, signs of hepatic inflammation, and pancytopenia [95]. TRGVHD occurs in patients with severe defects of cellular immunity, most notably HSCT patients, neonates, and patients with lymphoproliferative disorders. Transfusion from relatives and HLA compatible donors are at risk of causing GVHD. It can be prevented by gamma irradiation of cellular blood components.

Immune Modulation

Transfusions have been known to induce immune tolerance following the observation made more than 20 years ago that multiply transfused kidney transplant recipients had an increased graft survival rate [96]. Transfusion-induced immunosuppression has been implicated in postoperative infection, increased cancer recurrence rates, and development of non-Hodgkin lymphoma [97,98]. There is also evidence from animal studies

TABLE 114.3

RANDOMIZED CLINICAL TRIALS IN TRANSFUSION MEDICINE THAT HAVE RESULTED IN CHANGES IN CLINICAL PRACTICE

Appropriate hemoglobin threshold for RBC transfusion	Hebert et al. [18] Hebert et al. [19] (The TRICC Trial)	A hemoglobin threshold of 7.0 g/dL vs. 9.0 g/dL is not associated with increased morbidity, mortality, or prolonged ventilatory support.
Appropriate platelet count threshold for prophylactic platelet transfusion	Gmur et al. [35] Wandt et al. [36] Rebulla et al. [37]	Platelet transfusion "triggers" of < 10,000/μL are safe for the prevention of bleeding in chemotherapy-induced thrombocytopenia in patients without comorbid conditions.
Prevention of transfusion transmitted CMV infection	Bowden et al. [80]	Leukocyte reduction of cellular blood components is as effective in reducing the risk of CMV transmission as the use of CMV seronegative blood components.
Prevention of platelet alloimmunization	TRAP Study Group [51]	Leukoreduction of cellular blood components prevents HLA alloimmunization in patients with acute leukemia undergoing induction chemotherapy.
Use of leukoreduction to decrease postoperative infection	van de Watering et al. [99]	Leukoreduction of cellular blood components decreases postoperative infection in patients undergoing cardiac surgery.
Appropriate platelet transfusion dose for prophylactic transfusion of thrombocytopenia	Slichter et al. [49]	Low-dose platelet transfusion results in an overall decrease in the number of total platelets transfused and no increase in bleeding. Platelet transfusion frequency is increased.

that transfusion increases the risk of metastatic disease, although data in humans are inconclusive. Removal of donor leukocytes has been shown to decrease the immunomodulatory effects of blood transfusions. The clinical usefulness is clear only in prevention of alloimmunization in patients undergoing chemotherapy for acute myelocytic leukemia [50]. A prospective randomized study in patients undergoing cardiac surgery showed a decrease in infection rates when leukocyte-reduced blood components were used [99]. This has led some centers to adopt policies of universal leukoreduction, but this remains controversial.

Table 114.3 summarizes some of the most important recent advances in transfusion medicine based on randomized, controlled trials or meta-analyses of such trials.

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CHAPTER 115 ■ CRITICAL CARE OF PATIENTS WITH HEMATOLOGIC MALIGNANCIES

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INTRODUCTION

Although the incidence of aggressive hematologic malignancies like acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and intermediate- and high-grade non-Hodgkin lymphomas is low, these potentially curable diseases frequently require intensive care unit (ICU) management at presentation to prevent early mortality and achieve disease remission. Patients with hematologic malignancies account for approximately 2% of all ICU admissions [1,2]. Approximately 7% of patients with hematologic malignancies admitted to the hospital will become critically ill [3]. The most frequently reported indications for ICU admission in patients with hematologic malignancies are respiratory failure (26% to 91%), severe sepsis (8% to 64%), neurologic impairment (14% to 23%), and acute renal failure (14% to 23%). For all critically ill patients with hematologic malignancies, ICU mortality, in hospital mortality and 6-month mortality rates are 23% to 62%, 54% to 82%, and 66% to 83%, respectively [1–11]. Risk factors for death in the ICU include high disease severity score (APACHE II, SAPS II, SOFA), vasopressor use, leukopenia, increasing number of organ failures, and acute renal failure (see Table 115.1). Notably, mechanical ventilation has not been consistently associated with increased risk of death in this patient population, and some studies suggest improved outcomes with early endotracheal intubation [2,12]. In addition, survival in patients with hematologic malignancies admitted to the ICU after chemotherapy alone versus hematopoietic stem cell transplant (HSCT) are not different, suggesting that critically ill HSCT patients should be treated aggressively on ICU admission [13,14]. In fact, when matched for severity of acute illness upon ICU admission, survival of patients with hematologic malignancies and nononcologic patients appears to be similar [1].

OVERVIEW OF HEMATOLOGIC MALIGNANCIES

Acute Myeloid Leukemia

AML accounts for 22% to 54% of hematologic malignancy admissions to the ICU [1,2,4,6–11]. Patients with AML may require ICU admission for disease- or treatment-related complications including sepsis (frequently complicated by neutropenia), bleeding due to thrombocytopenia and occasionally acute disseminated intravascular coagulation and multiple organ failure.

The incidence of AML in the United States is 3.5 cases per 100,000 persons per year with approximately 12,000 new cases diagnosed annually [15]. More than half of newly diagnosed AML patients are over 65 years of age and a third are older than 75 years. Five-year survival rates are approximately 50% in adults under the age of 45 years but drop to less than 10% in patients over the age of 65 [16]. The risk factors for the development of AML, including genetic and environmental factors, have been well defined [17–27].

AML arises from the acquisition of genetic mutations in myeloid precursors or stem cells leading to various degrees of maturation arrest, unregulated proliferation, and resistance to apoptosis. By the World Health Organization 2008 classification system, the diagnosis of AML requires myeloid blasts to comprise 20% or more of nucleated cells in the peripheral blood or bone marrow except in cases of AML with the recurrent cytogenetic abnormalities t(15;17), t(8;21), inv(16)/t(16;16), myeloid sarcoma (a tumor of myeloblasts), and some cases of erythroleukemia [28]. The recurrent cytogenetic abnormalities t(15;17), t(8;21), inv(16)/t(16;16) and normal cytogenetics accompanied by gene mutations in NPM1 or CEBP-alpha confer a better prognosis in terms of risk of relapse, and the majority of patients obtain durable complete remissions with chemotherapy alone [28,29]. Conversely, patients with poor-risk cytogenetics and those with normal cytogenetics accompanied by mutations in the FLT3 proto-oncogene have a low likelihood of durable remission with chemotherapy alone and typically undergo allogeneic HSCT [29].

Standard induction chemotherapy for AML using 3 days of intravenous (IV) anthracycline (daunorubicin, idarubicin) or anthracenedione (mitoxantrone) and 7 days of cytarabine by continuous IV infusion, ideally initiated within 5 days of diagnosis, leads to complete remission rates of 60% to 80% in young adults under 60 years of age and 50% in patients over 60 years of age. Postremission therapy is tailored to pretreatment risk status, performance status and age and may consist of three to four cycles of high-dose cytarabine, autologous HSCT or, for younger patients at high risk of relapse, allogeneic HSCT [30].

Acute Promyelocytic Leukemia

APL accounts for 5% to 6% of all acute myeloid leukemia with approximately 600 to 800 new diagnoses made each year in the Unites States [31,32]. APL frequently presents with acute disseminated intravascular coagulation (DIC) that can be rapidly fatal due to intracerebral, pulmonary, or gastrointestinal hemorrhage, in all accounting for 50% to 60% of early deaths [33]. Early suspicion and treatment of APL, even prior to definitive genetic diagnosis, is important to reduce the risk of life-threatening hemorrhage [34]. Paradoxically, patients are also at risk for thrombotic events that complicate about 10% to 12% of cases, frequently in those with expression of CD2, CD15, and FLT3-ITD mutation [35,36].

APL occurs due to arrest of myeloid differentiation at the promyelocyte stage leading to accumulation of leukemic promyelocytes in the bone marrow, blood, and tissues. Morphologically, leukemic promyelocytes typically have variable

TABLE 115.1

OUTCOMES OF PATIENTS WITH HEMATOLOGIC MALIGNANCIES ADMITTED TO THE ICU

Number of patients	ICU mortality (%)	In-hospital mortality (%)	Risk factors for death	Reference
7,689	43	59	HSCT, Hodgkin lymphoma, severe sepsis, age, length of hospital stay prior to ICU admission, respiratory failure, neurologic failure, renal failure, anemia	[2]
22	55	82	APACHE II score, number of failing organs, mechanical ventilation	[4]
60	—	78	APACHE II score > 30, number of failing organs, resistant disease, leukopenia	[5]
92	—	77	Progression of underlying malignancy	[6]
78	26	—	Number of failing organs, liver failure	[7]
104	44	—	SAPS II score, mechanical ventilation	[8]
124	42	54	Leukopenia, vasopressors, renal failure	[9]
58	62	—	SAPS II score, SOFA score	[10]
24	—	75	SAPS II score > 66, liver failure, neurologic failure, number of failing organs	[3]
92	50	55	SAPS II, SOFA, ODIN, and LODS scores, allogeneic HSCT, neutropenia, severe sepsis, vasopressor use, invasive mechanical ventilation	[11]
101	23	—	SAPS II score, SOFA score, mechanical ventilation, renal replacement therapy	[1]

HSCT, hematopoietic stem cell transplant; SAPS II, Simplified Acute Physiology Score II; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ODIN, Organ Dysfunction and/or Infection Score; LODS, Logistic Organ Dysfunction Score.

nuclear morphology with bilobed or reniform nuclei, prominent cytoplasmic granules, and numerous large Auer rods, frequently in bundles [37]. Approximately 5% of APL presents as a microgranular variant characterized by few or absent granules [38]. Patients with this microgranular variant tend to have higher presenting white blood cell counts, placing them at higher risk for complications and relapse. Except in rare instances, APL is characterized by the presence of the recurrent cytogenetic abnormality t(15;17)(q22;q12) leading to a PML-RAR-alpha fusion gene that can be demonstrated by cytogenetic analysis, FISH and quantitative RT-PCR [37]. The chimeric PML-RAR-alpha protein is the target of therapy with all-*trans*-retinoic acid (ATRA) and arsenic trioxide (ATO), agents that cause degradation of the PML-RAR-alpha oncoprotein thereby promoting terminal differentiation of leukemic promyelocytes [39,40].

The diagnosis of APL should be considered in any patient with a new diagnosis of leukemia especially if accompanied by clinical and laboratory evidence of acute DIC. Early institution of treatment with the differentiating agent ATRA is indicated upon suspicion of APL [32,34]. Careful review of the peripheral blood smear from new leukemia patients in consultation with hematologists and hematopathologists should be performed to look for characteristic hypergranular leukemic promyelocytes. Expedited performance of flow cytometry, specifically evaluating for coexpression of CD34, CD15, and CD13 on the surface of leukemic cells can aide in diagnosing the microgranular variant of APL [41].

Greater than 70% of APL patients attain prolonged remissions with current treatment strategies. Induction chemotherapy regimens generally combine ATRA with an anthracycline, typically idarubicin or daunorubicin [32]. ATO is highly active against APL and in combination with ATRA produces CR rates over 90% [42–44]. ATRA or ATO, however, may cause a fatal differentiation syndrome characterized by fever, dyspnea, pulmonary infiltrates, pleuropericardial effusions, weight gain, peripheral edema, renal failure, and hypotension.

Acute Lymphoblastic Leukemia

ALL results from the acquisition of genetic mutations in lymphoid progenitor or stem cells resulting in the arrest of cells at an early stage of differentiation [45]. In 2009, about 5,760 people were diagnosed with ALL in the United States with a median age of 13 years [15]. ALL patients comprise 9% to 27% of ICU admissions for hematologic malignancies [1,2,4,6–11]. The 10-year survival among adults with ALL is less than 30% [45–47]. Favorable disease characteristics in ALL include ages 1 to 15 years, presenting WBC < 50,000 per μL and rapid achievement of complete remission, whereas age > 35 years is unfavorable. Cases with the t(9;22)/BCR-ABL (Philadelphia chromosome, Ph), representing 15% to 20% of adult cases of ALL, and the t(4;11)/MLL-AF4 translocations typically fare poorly, with survival rates of less than 10% with chemotherapy alone and long term survival after allogeneic HSCT ranging 20% to 45% [48–53].

Clinical trial regimens in the last decade have improved complete remission rates to 74% to 93% with 5-year survival rates as high as 48% [54]. Therapy for ALL typically spans 2 to 3 years and includes induction therapy, postremission therapy, central nervous system (CNS) prophylaxis and maintenance chemotherapy in patients who do not undergo HSCT. Induction therapy for ALL typically combines vincristine, an anthracycline (e.g. daunorubicin), and a corticosteroid (prednisone or dexamethasone) with l-asparginase and/or cyclophosphamide. Prophylaxis against CNS relapse includes intrathecal chemotherapy with methotrexate with or without cytarabine and frequently high-dose IV systemic methotrexate. Postremission therapy typically includes the same agents used in induction as well as cytarabine and 6-mercaptopurine. Maintenance therapy consists of oral methotrexate and 6-mercaptopurine often with pulses of vincristine and corticosteroids. Imatinib (Gleevec®) and dasatinib (Sprycel®) inhibit the chimeric BCR-ABL tyrosine kinase produced by the Philadelphia

chromosome and improve complete remission and survival rates in Ph+ ALL [55–63]. Ideally, allogeneic HSCT is performed in patients with poor-risk disease.

Aggressive Non-Hodgkin Lymphomas

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma of intermediate grade that typically presents with rapidly enlarging lymph nodes or extranodal masses frequently with symptoms of organ compromise from lymphomatous involvement of extranodal sites. Diagnosis is typically made by excisional biopsy of a lymph node or mass showing large lymphoid cells that completely efface lymph node architecture. Malignant B-cells express CD19, CD20, and CD22 with variable expression of surface immunoglobulin, CD5 and CD10 [64]. Common genetic abnormalities in DLBCL include constitutive expression of the transcriptional repressor Bcl-6, the antiapoptotic protein Bcl-2, and/or the transcription factor c-myc [65]. The International Prognostic Index for aggressive lymphomas uses five unfavorable variables to establish risk status: age greater than 60 years, poor performance status, advanced stage (Ann Arbor Stage III or IV disease), extranodal involvement at more than one site and elevated serum lactate dehydrogenase [66]. First-line combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in combination with the humanized monoclonal anti-CD20 antibody rituximab results in 2-year overall survival rates of 70% to 90% [65].

Burkitt lymphoma (BL), which has the fastest growth rate of any human malignancy, is an aggressive non-Hodgkin lymphoma with endemic, sporadic, and immunodeficiency-associated clinical variants. BL typically presents with rapidly progressive nodal and extranodal disease, commonly in the abdomen and gastrointestinal tract leading to nausea, vomiting, anorexia, bowel obstruction, and gastrointestinal bleeding. Advanced stage is common at diagnosis with bone marrow involvement in 30% to 38% and CNS involvement in 13 to 17% of adults [67]. Morphologically, lymphoma cells are medium-sized with deeply basophilic cytoplasm containing cytoplasmic lipid vacuoles and a high proliferative index of greater than 90%. A leukemic variant exists and can be distinguished from ALL by surface expression of immunoglobulin, CD20 and CD10, without coexpression of TdT or CD34. BL is genetically characterized by chromosomal translocations that lead to constitutive expression of c-myc, typically t(8;14) and rarely t(2;8) or t(8;22)[68]. High-intensity, brief-duration chemotherapy, typically with cyclophosphamide, doxorubicin, vincristine, and antimetabolite-containing regimens, with intensive CNS prophylaxis, have led to 1-year remission rates as high as 86% [67]. The bulky disease and high cell proliferation rates seen in both DLBCL and Burkitt lymphoma place patients at high risk for tumor lysis syndrome and prophylactic treatment with allopurinol to prevent hyperuricemia is typically given prior to chemotherapy.

Other Malignancies

Other notable hematologic malignancies frequently requiring ICU level care are multiple myeloma, Waldenstrom macroglobulinemia and myeloproliferative neoplasms such as chronic myeloid leukemia, essential thrombocythemia, polycythemia vera, and chronic idiopathic myelofibrosis. In multiple myeloma, spinal cord compression may occur due to encroachment of the spinal canal by epidural plasmacytomas and from pathologic fracture of spinal vertebrae. Emergent imaging of the entire spine with MRI is required for diagnosis (see Chapter 116). In Waldenstrom macroglobulinemia, high concentrations of monoclonal IgM paraprotein in the serum can lead to the hyperviscosity syndrome manifest as mucosal bleeding, confusion, seizures, coma, visual disturbance, and/or headache as well as cryoglobulinemia, cold agglutinin hemolytic anemia, and plasma volume expansion leading to congestive heart failure [69]. Myeloproliferative neoplasms may lead to life-threatening hemorrhage or thrombosis, requiring critical care (see Chapter 111).

DISEASE AND TREATMENT RELATED COMPLICATIONS

Hyperleukocytosis and Leukostasis

In AML, hyperleukocytosis, generally defined as a circulating blast count greater than 50,000 to 100,000 per μL, occurs in 5% to 18% of patients at initial presentation [70,71]. Early mortality during initial treatment of patients with hyperleukocytic AML ranges from 5% to 30% with advanced age, poor performance status, coagulopathy, respiratory compromise, and organ failure associated with early death [70–75]. Hyperleukocytosis in AML is frequently associated with leukostasis manifesting as respiratory failure, visual disturbance, intracranial hemorrhage, and renal failure.

Leukostasis, although typically associated with hyperleukocytosis, can occur at white blood cell counts less than 50,000 per μL (likely due to interpatient variability in leukemia cell biology and individual susceptibility). Myeloid leukemic blasts are less deformable than mature white blood cells possibly predisposing to formation of aggregates of cells in the small blood vessels, tissue ischemia, endothelial damage and tissue infiltration [76–78]. In addition, expression of specific cell surface adhesion molecules on leukemia cells and endothelial cell activation by cytokines secreted by leukemic blasts may play important roles in promoting leukostasis. The expression of CD56/NCAM on the surface of leukemia cells in myelomonocytic AML correlates with the development of leukostasis [79]. In vitro, myeloid blasts promote their own adhesion to the vascular endothelium by upregulating expression of ICAM-1, VCAM-1, and E-selectin on endothelial cells [80]. In ALL, hyperleukocytosis is rarely associated with symptomatic leukostasis except with extreme hyperleukocytosis (WBC > 400,000 per μL) possibly due to the smaller size, easier deformability, and decreased vascular endothelium adherence of lymphoblasts [81]. Notably, lymphoblasts in the rare ALL patients with symptomatic leukostasis are less deformable than lymphoblasts from ALL patients without leukostasis [82]. In AML with hyperleukocytosis, most studies have not shown a demonstrable difference in complete response rates, disease free survival or overall survival after treatment [83]. However, the presence of pulmonary leukostasis, hepatomegaly, hyperbilirubinemia, and hypofibrinogenemia are predictors of poor outcome in patients with hyperleukocytosis [74,75,84].

Hydroxyurea at doses of 20 to 30 mg per kg per day or more can reduce peripheral leukocyte counts, and generally requires 1 to 2 days to take effect. Red blood cell transfusions should be avoided until the leukocyte count is less than 50,000 per μL to avoid ischemic events such as stroke or acute coronary syndrome. Although invasive, leukapheresis is a relatively safe procedure and is frequently used in combination with hydroxyurea to rapidly lower circulating blast counts and theoretically decrease the risk of tumor lysis syndrome and progressive leukostasis. Two blood volumes (140 mL per kg) are processed in the typical leukapheresis procedure. Studies have failed to show a consistent clinical benefit with the use of leukapheresis in hyperleukocytic leukemias [85–88], although some uncontrolled retrospective single institution studies show reduction

of early mortality in patients undergoing leukapheresis without an overall survival benefit [87,88]. Despite the poor prognosis of APL presenting with hyperleukocytosis and organ failure, leukapheresis is contraindicated in this group of patients due to risk of exacerbating acute DIC, initiating vasomotor instability, and increasing induction death [89].

Hyperviscosity Syndrome

The hyperviscosity syndrome occurs in 30% of patients with Waldenstrom macroglobulinemia (also called lymphoplasmacytic lymphoma with IgM monoclonal gammopathy) at presentation and is defined by the presence of increased serum viscosity with neurologic symptoms related to impaired blood flow including headache, vertigo, dizziness, visual impairment, hearing impairment, tinnitus, nystagmus, stupor, stroke, dementia, and coma [90–95]. In addition, mucosal bleeding, including GI hemorrhage, renal failure, and congestive heart failure due to plasma volume expansion and concomitant anemia may occur. Elevated serum IgM, with its large pentameric structure, is most commonly associated with hyperviscosity, although the syndrome has been reported with IgA, IgG, and kappa light chain multiple myeloma [96–101]. Normal serum viscosity measures 1.4 to 1.8 centipoises [102,103] and symptomatic hyperviscosity typically occurs at greater than 4 centipoises [69].

Emergent plasmapheresis is indicated for symptomatic hyperviscosity. One to two plasma volumes are typically exchanged and replaced with 5% albumin in patients with low bleeding risk or fresh frozen plasma (FFP) in patients at high risk for bleeding. Symptoms typically resolve quickly but neurologic deficits can remain. Red blood cell transfusions should be avoided if possible until serum viscosity is lowered. Definitive treatment for the underlying malignancy should be instituted quickly to control paraprotein production. Procedural risks include depletion of clotting factors when 5% albumin is used as the exchange fluid, hypocalcemia from citrate anticoagulant use, dialysis catheter-related infection, pneumothorax or thrombosis, and complications from FFP administration including anaphylaxis, blood-borne infections, and transfusion-related acute lung injury.

Bleeding

Bleeding in hematologic malignancies is a common cause of morbidity and mortality. DIC and thrombocytopenia are common etiologies, but acquired clotting factor deficiencies can also predispose to life-threatening hemorrhage.

Disseminated Intravascular Coagulation

Acute DIC is a common cause of morbidity and mortality during the treatment of many hematologic malignancies and is especially characteristic of acute promyelocytic leukemia and to a lesser degree other forms of acute leukemia. Sepsis, especially gram-negative sepsis occurring in the setting of disease or treatment related neutropenia, is a common cause of DIC as well. Complicating the diagnosis of DIC is the frequent presence of hepatic failure due to malignant infiltration of the liver or treatment-related hepatotoxicity. Clinically, patients are at high risk for death from bleeding and can develop oozing from IV lines and surgical sites, purpura, pulmonary hemorrhage, intracranial hemorrhage, gastrointestinal bleeding, and multiple organ failure.

Acute DIC results from pathologic coagulation within small blood vessels, typically from the release of tissue factor or endotoxin exposure, leading to unmitigated activation of coagulation and consumption of coagulation factors and platelets. Depletion of clotting factors and platelets, activation of plasmin, and the production of anticoagulant fibrin split products can lead to severe bleeding. Laboratory hallmarks of acute DIC include thrombocytopenia, prolongation of clotting times, hypofibrinogenemia, elevated fibrin split products, and sometimes schistocytes on the peripheral blood smear.

The coagulopathy observed in APL resembles acute DIC but with some subtle differences [104]. In APL, leukemic cells produce tissue factor and high levels of a cysteine protease called cancer procoagulant, both of which are downregulated by ATRA treatment in primary and cultured leukemic APL blasts [105–109]. Tissue factor in conjunction with activated Factor VII activates Factor X, whereas cancer procoagulant can directly activate Factor X leading to pathologic coagulation [104,110]. In addition, rapid death of malignant cells leads to increased thrombin generation [111]. Unlike acute DIC, antithrombin and protein C levels are maintained in the coagulopathy of APL [112]. Increased fibrinolysis also complicates APL and can lead to bleeding. APL cells express both cell surface u-PA (urokinase-plasminogen activator) and t-PA (tissue-plasminogen activator). u-PA is transiently upregulated upon differentiation of leukemic cells with ATRA [113,114]. Dexamethasone administered with ATRA suppresses the upregulation of u-PA. Annexin II is highly expressed on leukemic promyelocytes and interacts with plasminogen and t-PA to increase plasmin production [115]. In addition, annexin II is highly expressed on cerebral endothelial cells potentially explaining the high rates of intracerebral hemorrhage in APL [116,117]. Notably, treatment with ATRA downregulates the expression of annexin II on leukemic promyelocytes [115,118].

Reversal of acute DIC requires effective treatment of the underlying cause. Supportive care includes early management of sepsis including the administration of broad-spectrum antibiotic coverage with anti-Pseudomonal activity in neutropenic patients and reversal of organ dysfunction when possible. In the setting of APL, early institution of ATRA combined with cytotoxic chemotherapy in high-risk patients with WBC $> 10{,}000$ per μL is indicated to reduce the burden of leukemic promyelocytes. DIC typically resolves within 48 hours of initiation of ATRA in this setting.

With acute DIC, frequent monitoring of complete blood count, prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen three to four times a day is prudent to monitor the consumptive process and guide replacement of platelets and coagulation factors. In patients with APL-associated DIC who are bleeding or who are at high risk of bleeding, maintenance of platelet count above 30,000 to 50,000 per μL and fibrinogen above 100 to 150 mg per dL with platelet and cryoprecipitate transfusions has been recommended [32]. Fresh frozen plasma also may be given to reduce the prolonged PT and PTT. By inhibiting thrombin and Factor Xa, low-dose heparin (4 to 5 U per kg per hour) could theoretically improve severe bleeding in acute DIC by limiting fibrinogen and platelet consumption, plasminogen activation, and fibrin split product production. Results of clinical studies, however, have been equivocal, and routine use of heparin to prevent or treat acute DIC-related bleeding is not universally standard [104,119–121]. Conversely, thrombosis may occur in acute DIC, and in this setting, the administration of low-dose heparin may beneficial [122,123].

Thrombocytopenia

Thrombocytopenia in patients with hematologic malignancies can be caused by bone marrow infiltration by malignant cells, myelosuppression from chemotherapy and other medications, bacterial sepsis, acute DIC, immune thrombocytopenia and/or hypersplenism from splenomegaly. The risk of major

hemorrhage dramatically increases at platelet counts less than 5,000 per μL and the use of prophylactic platelet transfusions, starting in the 1970s, typically with a transfusion threshold of 20,000 per μL, reduced the frequency of fatal bleeding in this population to less than 1%. However, this strategy led to an increased demand for platelet concentrates [124,125].

The issue of the optimal platelet count to trigger a prophylactic platelet transfusion has been addressed. A 2004 Cochrane Database systematic review included three prospective randomized studies comparing prophylactic platelet transfusions at platelet counts of 10,000 per μL versus 20,000 per μL. None of these studies showed significant differences in severe bleeding events or mortality but the studies were small and possibly underpowered to show noninferiority of the lower transfusion threshold [125]. Current studies suggest that the risk of spontaneous hemorrhage in patients without concomitant coagulopathy or acute DIC, platelet dysfunction, fever, mucositis or uncontrolled hypertension is acceptable until platelets are below 10,000 per μL. Safely minimizing the platelet dose per prophylactic transfusion has recently been studied. A 2010 study randomized 1,272 patients undergoing chemotherapy or HSCT for hematologic and nonhematologic malignancies to receive 1.1×10^{11}, 2.2×10^{11}, or 4.4×10^{11} platelets per square meter of body surface area to be given prophylactically for platelet counts less than 10,000 per μL. The lowest dose group required fewer platelets overall but required more transfusions (five versus three per patient per treatment course). Bleeding rates of all grades were similar between the groups with no deaths from hemorrhage in the low- and medium-dose groups supporting the use of low-dose platelet transfusions [126]. Avoiding drugs that cause platelet dysfunction (especially aspirin, nonsteroidal anti-inflammatory agents [NSAIDs], Cox-2 inhibitors, and clopidogrel), treating underlying coagulopathy and reversing renal dysfunction are important adjuncts to preventing bleeding in thrombocytopenic patients as well.

Acquired von Willebrand Syndrome

The acquired von Willebrand syndrome (aVWS) results from a reduction in the level of von Willebrand factor (VWF) and may rarely occur in monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom macroglobulinemia, multiple myeloma, non-Hodgkin lymphomas, and myeloproliferative neoplasms, especially essential thrombocythemia [127–130]. Treatment of the underlying malignancy to decrease tumor burden or reduce elevated platelet counts is generally effective in resolving acquired von Willebrand disease. Management may include platelet apheresis in the setting of extreme thrombocytosis and active bleeding [131]. High-dose IVIG (dose, 1 g per kg per day for 2 days) may be considered in patients with lymphoid neoplasms who have inhibitory antibodies to VWF [99,100,132,133]. For treatment of acute bleeding, desmopressin (dose, 0.03 μg per kg IV) or purified plasma-derived vWF/FVIII concentrates may be considered [132]. Aspirin and NSAIDs should be avoided until the aVWS has resolved.

Pulmonary Complications

Mechanical ventilation is associated with poor outcomes in patients with hematologic malignancies. Mortality ranges from 39% to 82%, although most studies of respiratory failure in patients with hematologic malignancies are retrospective and have failed to match mechanically ventilated and nonventilated patients for degree of respiratory compromise. Hampshire et al. retrospectively studied 7,689 cases of hematologic malignancies requiring ICU admission in England, Wales, and Northern Ireland. When matched for PaO_2:FiO_2 ratios, mechanically ventilated hematologic malignancy patients had reduced mortality compared with nonventilated hematologic malignancy patients (mortality 67% vs. 85% for PaO_2:FiO_2 < 100 mm Hg, 50% vs. 69% for PaO_2:FiO_2 100 to 199 mm Hg)[2]. In a smaller study, invasive mechanical ventilation within 24 hours after ICU admission was associated with lower mortality rates compared with patients receiving noninvasive positive pressure ventilation [12]. After HSCT, however, patients who require mechanical ventilation appear to fare less well. Short-term mortality is 82% to 96% and worsens to 98% to 100% in the setting of combined renal and hepatic failure [101]. Only 9% to 14% of mechanically ventilated HSCT patients are alive 6 months after ICU admission [93,101].

Diagnostic approaches to identify the etiology of respiratory failure include blood cultures, blood and urine infectious serologies, diagnostic imaging, bronchoscopy, and surgical lung biopsy. Flexible bronchoscopy with bronchoalveolar lavage (BAL) detects pulmonary infections in approximately 50% of patients with hematologic malignancies presenting with respiratory deterioration leading to a change in antimicrobial therapy in 38% of patients [94,95]. In one study there was no survival advantage to BAL and respiratory deterioration requiring mechanical ventilation occurred in 36% of patients as a short-term consequence of BAL highlighting the need for careful patient selection and the broad use of noninvasive diagnostic tests prior to pursuing BAL [95]. In two retrospective studies of surgical lung biopsy among hematologic malignancy patients with unexplained pulmonary infiltrates, a specific diagnosis was made in 62% to 67% of patients and led to change in therapy 40% to 57% of the time. A specific diagnosis was significantly associated with decreased mortality in both studies (absolute reduction in mortality, 29% to 33%) [103,134].

Infection is the most common identifiable cause of respiratory distress in hematologic malignancies. Pulmonary hemorrhage, diffuse alveolar damage, pulmonary embolism, and congestive heart failure are the most common identifiable noninfectious causes. Pulmonary infections are typically due to *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and streptococcal species with *Legionella pneumophila* and mycobacterial infections being less common pathogens. Prolonged neutropenia from underlying disease or myelotoxic chemotherapy places patients at risk for mycelial fungal pneumonia with *Aspergillus* spp being the most common offenders. Patients with lymphoid malignancies and those treated with allogeneic HSCT are also at risk for *Pneumocystis jiroveci* pneumonia and viral pneumonias including cytomegalovirus infection. Effective antimicrobial treatment can be difficult in this group of patients as mixed infections and antimicrobial resistance are common [135,136]. Ganciclovir and related antiviral agents in combination with IV immunoglobulin have reduced the mortality of CMV pneumonia in HSCT patients [137].

Noninfectious etiologies of respiratory failure in patients with hematologic malignancies, including those undergoing HSCT, include cardiogenic pulmonary edema, diffuse alveolar hemorrhage, engraftment syndrome, idiopathic pneumonia syndrome, bronchiolitis obliterans syndrome (BOS), cryptogenic organizing pneumonia, granulomatous inflammation and malignant infiltration of the lungs. Chemotherapeutic agents such as carmustine (BCNU), busulfan, and bleomycin are known to cause lung injury. ICU patients with hematologic malignancies are also at high risk for pulmonary embolism given immobility, active malignancy, and frequently DIC.

Diffuse alveolar hemorrhage (DAH) accounts for 20% to 30% of pulmonary complications after allogeneic HSCT [138] and is a cause of early death in 1.5% of patients with APL [33]. DAH occurs with hematopoietic engraftment in allogeneic HSCT patients and presents with cough, hemoptysis, declining hemoglobin, and hypoxemia with diffuse alveolar filling on lung imaging. Serial lavage during BAL shows increasingly bloody fluid return. Treatment for DAH includes

replacement of platelets and coagulation factors to maintain hemostasis, supportive mechanical ventilation as needed, and corticosteroids. Small retrospective studies support the use of high-dose corticosteroids (methylprednisolone 30 to 1,500 mg per day) for treatment of DAH after allogeneic HSCT [139–141]. Administration of parenteral recombinant activated factor VII has been associated with resolution of DAH occurring after HSCT in several case reports [142–147].

In addition to DAH, early onset noninfectious pulmonary complications after allogeneic HSCT include pulmonary engraftment syndrome and idiopathic pneumonia syndrome. Pulmonary engraftment syndrome mimics DAH and is characterized by fever, pulmonary infiltrates, hypoxia, and a skin rash developing early after HSCT, coinciding with recovery of circulating neutrophils (ANC > 500 per μL). It is typically a self-limited process lasting 1 to 2 weeks that is treated with supportive care and a short course of standard-dose corticosteroids [118]. Idiopathic pneumonia syndrome (IPS), which occurs in about 10% of HSCT patients, presents with fever, cough, shortness of breath, hypoxemia, and diffuse bilateral pulmonary infiltrates without an identifiable infection by BAL. IPS occurs after hematopoietic engraftment with a median onset of 21 to 52 days after HSCT and carries a 60% to 90% mortality [117,148,149]. Pathologically the syndrome is characterized by an interstitial infiltrate comprised primarily of lymphocytes. In a study of 15 patients with IPS, the combination of etanercept, a tissue necrosis factor-alpha (TNF-alpha) antagonist, and corticosteroids given at 2 mg per kg daily (methylprednisolone equivalent) resulted in 10 complete responses and a 28-day survival of 73% [150].

Late-onset noninfectious pulmonary complications after HSCT typically occur more than 3 months after stem cell infusion and include BOS and cryptogenic-organizing pneumonia (COP, formerly referred to as bronchiolitis obliterans with organizing pneumonia). BOS occurs in 14% of allogeneic HSCT patients with chronic graft-versus-host disease (cGVHD). BOS is a manifestation of cGVHD whereby alloreactive donor T-cells generate fibromuscular proliferation of the walls of small airways. This produces an obstructive physiology with air trapping and occasionally the need for supplemental oxygen. There is no standard treatment for BOS beyond immunosuppression for cGVHD, although investigations are ongoing combining aerosolized corticosteroids with azithromycin and montelukast (a leukotriene receptor antagonist). COP tends to occur late after allogeneic HSCT and demonstrates restrictive pulmonary physiology. COP is associated with GVHD and may be a manifestation of the disease itself. Some insult triggers inflammation of the small airways causing a proliferative bronchiolitis and deposition of cellular matrix materials into alveoli leading to hypoxemia. Unlike BOS, COP is reversible and corticosteroid responsive [151].

Common pulmonary processes complicating hematologic malignancies are summarized in Table 115.2.

Infection

Chemotherapy for high-grade hematologic malignancies commonly causes neutropenia (phagocytic immunocompromise) and cellular and/or humoral immunosuppression. For uncertain reasons, AML patients retain adequate cellular and humoral immunity even during periods of severe bone marrow suppression. Neutropenic patients are susceptible to infections by endogenous skin, genitourinary and gastrointestinal tract flora as well as hospital-acquired infections including nosocomial and ventilator-associated pneumonias, central venous line infections, *Clostridium difficile* colitis, and infections with *Pseudomonas* spp, *Stenotrophomonas* spp, *Burkholderia* spp, vancomycin-resistant enterococcus, methicillin-resistant *S. aureus*, and extended spectrum beta-lactamase-producing Gram-negative organisms. Prolonged neutropenia, especially with concomitant corticosteroid administration or diabetes mellitus, places patients at risk for invasive fungal infections, especially *Aspergillus* spp. Immunosuppressed patients, particularly those with lymphoid malignancies and those undergoing allogeneic HSCT, are at additional risk for opportunistic infections such as *P. jiroveci*, herpes simplex virus, varicella zoster virus, and cytomegalovirus. Treatment of febrile patients with neutropenia or immunosuppression involves rapid evaluation for infectious causes and initiation of empiric broad-spectrum antibiotic therapy with adequate coverage of *Pseudomonas aeruginosa* and methicillin-resistant *S. aureus*. For patients with persistent fever and prolonged neutropenia (>7 days), the addition of antifungal therapy targeting *Aspergillus* spp is indicated. Afebrile neutropenic patients with an absolute neutrophil count less than 500 per μL should receive daily prophylactic treatment with a fluoroquinolone antibiotic. A meta-analysis of 95 trials including 52 trials using fluoroquinolone prophylaxis showed that neutropenic patients receiving fluoroquinolone prophylaxis had significant decreases in all cause mortality, infection-related mortality, fever and documented infection with a nonsignificant trend toward increasing antimicrobial resistance [152]. The use of granulocyte stimulating growth factors (e.g., G-CSF) in patients receiving myelotoxic chemotherapy reduces total days of neutropenia and hospital length of stay without promoting tumor cell growth or affecting overall survival [153].

Differentiation Syndrome

Differentiation syndrome (DS), formerly referred to as retinoic acid syndrome, is a potentially fatal process of unclear mechanism (likely, detrimental cytokine storm) that occurs in 2% to 27% of APL patients treated with ATRA or arsenic trioxide [154]. Symptoms include fever, peripheral edema, weight gain more than 5 kg, pleuropericardial effusions, shortness of breath, interstitial pulmonary infiltrates, acute renal failure and hypotension after initiating APL treatment with the differentiating agents ATRA or arsenic trioxide. The diagnosis requires at least two of the above findings. Moderate DS is defined as having two to three of the above findings whereas severe DS has four or more findings [155]. Elevation of liver transaminases may also occur. Symptoms can develop at any time within the first 4 weeks of treatment with highest incidences in the first and third weeks of treatment. Risk factors for the development of severe DS include WBC > 5,000 per μL and elevated serum creatinine [154].

The diagnosis of DS is difficult at times as frequent complications of APL and its treatment, such as pneumonia, pulmonary hemorrhage, heart failure, acute renal failure, and sepsis, can mimic the syndrome. Early consideration of DS is important, however, so that prompt treatment with dexamethasone can be initiated. In both moderate and severe cases, dexamethasone is given at 10 mg PO or IV twice a day. Although no controlled studies of dexamethasone treatment have been published, since the inception of this practice the mortality rate from differentiation syndrome has dropped to less than 1% in recent studies. In moderate cases, ATRA and/or arsenic trioxide can be continued safely with close monitoring for worsening symptoms. In severe cases, ATRA and/or arsenic trioxide are held until symptoms resolve at which point it is generally safe to resume treatment. Administration of chemotherapy early in ATRA treatment has been shown to reduce the incidence if differentiation syndrome [156]. Patients with high suspicion of APL and a WBC > 10,000 per μL should be treated immediately with cytotoxic chemotherapy in addition to ATRA prior

TABLE 115.2

FREQUENTLY ENCOUNTERED PULMONARY COMPLICATIONS IN HEMATOLOGIC MALIGNANCIES

Complication	Context	Timing	Diagnosis	Management
Infection	Neutropenia	Variable: ≤7 days of neutropenia: bacterial, *Candida* spp >7 days of neutropenia: bacterial, fungal including *Aspergillus* spp	Blood cultures, fungal serologies, BAL, lung biopsy (transbronchial, VATS, open) CXR/CT/HRCT	Empiric antimicrobials may include coverage of MRSA, GNRs, *Pseudomonas* spp, typical and atypical bacterial pathogens, *Candida* spp, *Aspergillus* spp
	HSCT	After engraftment: viral including CMV, RSV, Herpesviridae, fungal, bacterial, mycobacterial, *Pneumocystis jiroveci*	Blood cultures, fungal serologies, respiratory virus DFA and PCR, CMV PCR (blood), BAL, lung biopsy (transbronchial, VATS, open) CMV shell culture, viral PCR, fungal, bacterial and mycobacterial cultures with BAL and lung biopsy CXR/CT/HRCT	Prophylaxis: Herpesviridae: Acyclovir/valacyclovir. PCP: TMP/SMX, dapsone, atovaquone or inhaled pentamidine Treatment: Empiric coverage of MRSA, GNRs, *Pseudomonas* spp, typical and atypical bacterial pathogens, *Candida* spp, *Aspergillus* spp pending diagnosis Targeted therapy for diagnosed infection
Diffuse alveolar hemorrhage	DIC, APL	Anytime until DIC resolves	Cough, hemoptysis, hemoglobin drop CXR/CT/HRCT: Diffuse ground glass opacities, consolidations BAL: Increasingly bloody return on serial lavage	DIC: Treat underlying cause Platelet goal >50,000/μL Fibrinogen goal >100–150 mg/dL HSCT: High-dose corticosteroids, platelet goal >50,000/μL, correct coagulopathy, consider recombinant activated factor VII
	HSCT	First 3–4 wk after transplant, around engraftment		
Drug toxicity	HSCT (Carmustine, Busulfan) Busulfan	3 mo–2 y after exposure	CXR/CT/HRCT: Ground glass opacities, interstitial pneumonitis PFTs: Decreased DLCO	Corticosteroids, supportive care
Pulmonary engraftment syndrome	HSCT	At count recovery (ANC >500/μL)	Associated findings: fever, rash	Self-limited lasting 1–2 wk Corticosteroids
Idiopathic pneumonia syndrome	HSCT	3 wk–4 mo after HSCT	CXR/CT/HRCT: Interstitial pulmonary infiltrate	Corticosteroids Consider etanercept
Cryptogenic organizing pneumonia	HSCT	Late (>100 d after HSCT)	CXR/CT/HRCT: Bilateral patchy alveolar filling, areas of ground glass opacities and consolidation PFTSs: Restrictive physiology	Corticosteroid responsive Reversible
Bronchiolitis obliterans syndrome	HSCT, chronic GVHD	Late (>100 d after HSCT)	CT/HRCT: Air trapping, bronchiolitis PFTs: Obstructive physiology	Treat underlying GVHD Irreversible, corticosteroids may slow progression

BAL, bronchoalveolar lavage; VATS, video-assisted thoracoscopic surgery, CXR, chest X-ray; CT, computed tomography; HRCT, high-resolution computed tomography; MRSA, methicillin-resistant *Staphylococcus aureus*; GNR, Gram-negative rod; HSCT, hematopoietic stem cell transplant; CMV, cytomegalovirus; RSV, respiratory syncytial virus; DFA, direct fluorescence assay; PCR, polymerase chain reaction; PCP, *Pneumocystis jiroveci pneumonia*; TMP/SMX, trimethoprim/sulfamethoxazole; DIC, disseminated intravascular coagulation; APL, acute promyelocytic leukemia; PFTs, pulmonary function tests; DLCO, diffusing capacity; ANC, absolute neutrophil count; GVHD, graft-versus-host disease.

to molecular diagnosis as these patients are at especially high risk for severe differentiation syndrome and death during induction therapy [157]. Even with improved recognition and treatment, 26% of patients in the LPA96 and LPA99 trials developing severe DS died during induction therapy, 11% from DS alone [154].

Therapeutic Agents

Treatment of aggressive hematologic malignancies typically requires toxic, myelosuppressive chemotherapy regimens. Patients are prone to life-threatening bacterial and

TABLE 115.4

SELECTED EVIDENCE-BASED APPROACHES FOR HEMATOLOGIC MALIGNANCIES

Clinical relevance	Comparison	Results	Reference
ICU outcomes			
Patients with hematologic malignancies have similar mortality to nononcologic patients when matched for disease severity.	Retrospective study of 101 consecutive ICU admissions of patients with hematologic malignancies vs. 3,808 nononcologic admissions.	Mortality of hematologic malignancy and nononcologic patients similar when matched for SAPS II score (OR = 0.59, 95% CI = 0.32–1.08, $p = 0.09$).	[1]
Hyperleukocytosis			
Improved short-term but not long-term survival with leukapheresis in hyperleukocytic AML.	Retrospective analysis of leukapheresis in 53 vs. no leukapheresis in 28 AML patients with hyperleukocytosis (WBC > 100,000/μL).	Reduced 21-day mortality in leukapheresis group vs. no leukapheresis (16% vs. 32%, $p = 0.015$). No difference in overall survival (median 6.5 vs. 7.5 months).	[88]
Prophylactic platelet transfusion			
Equivalent bleeding rates with platelet transfusion threshold 10,000/μL vs. 20,000/μL.	Meta-analysis of three prospective randomized trials.	No difference in mortality, remission rates, severe bleeding events or RBC transfusion requirements between two threshold levels. Studies potentially underpowered.	[125]
Noninvasive positive pressure ventilation			
Improved survival with addition of noninvasive positive pressure ventilation to standard care alone in patients with early hypoxemia.	Prospective, randomized trial of 52 immunosuppressed patients with fever, pulmonary infiltrates, and early hypoxemic respiratory failure treated with NIPPV vs. supplemental oxygen-based therapy alone.	NIPPV superior to supplemental oxygen based therapy alone for incidence of endotracheal intubation (2 vs. 20 patients, $p = 0.03$), serious complications (13 vs. 21, $p = 0.02$), death in the ICU (10 vs. 18, $p = 0.03$) and death in the hospital (13 vs. 21, $p = 0.02$).	[185]
Invasive ventilation			
Improved survival with early intubation of hypoxemic patients.	Retrospective analysis of 166 consecutive admits requiring mechanical ventilation with NIPPV vs. IMV.	Intubation within 24 hours of ICU admission associated with improved survival (OR = 0.29, 95% CI = 0.11–0.78). Survival equivalent between NIPPV and IMV when matched for SAPS II score.	[12]
Prophylactic antibiotics during neutropenia			
Use of prophylactic antibiotics in afebrile neutropenic patients improves survival and supports use of fluoroquinolone prophylaxis.	Meta-analysis of 100 trials (10,275 patients).	Compared to placebo, antibiotic prophylaxis associated with reduced risk of death (RR = 0.66, 95% CI = 0.54–0.81), infection related death (RR = 0.58, 95% CI = 0.45–0.74) and fever (RR = 0.52, 95% CI = 0.37–0.84). Fluoroquinolone prophylaxis with reduced all-cause mortality (RR = 0.52, 95% CI = 0.37–0.84).	[152]
Growth factors for neutropenia			
G-CSF shortens duration of neutropenia without improving overall survival.	Prospective, randomized trial of G-CSF vs. placebo following AML induction chemotherapy.	Neutrophil recovery 15% earlier in G-CSF treated patients ($p = 0.014$). No difference in complete remission rates or 6-mo survival.	[186]
Differentiation syndrome			
Early institution of chemotherapy after starting ATRA for APL reduces the incidence of differentiation syndrome.	Randomized, prospective analysis of rates of differentiation syndrome in APL patients with WBC < 5,000/μL treated with ATRA until complete remission followed by chemotherapy vs. ATRA with chemotherapy starting day 3.	Incidence of differentiation syndrome 18% in ATRA with delayed chemotherapy vs. 9.2% in ATRA with early chemotherapy ($p = 0.035$).	[156]

SAPS II, simplified acute physiology score II; AUC, area under the curve; CI, confidence interval; NIPPV, noninvasive positive pressure ventilation; IMV, invasive mechanical ventilation; OR, odds ratio; RR, relative risk; G-CSF, granulocyte colony-stimulating factor; ATRA, all-trans-retinoic acid; APL, acute promyelocytic leukemia.

fungal infections as a result of prolonged neutropenia, bleeding from thrombocytopenia, and organ failure from the toxic effects of chemotherapy. Selected toxicities of agents commonly used in the treatment of hematologic malignancies and their management are supplied in Table 115.3.

Additional complications of malignant hematologic diseases or their treatment, including tumor lysis syndrome and malignant epidural cord compression, are discussed in detail in Chapter 116.

Selected evidenced-based approaches for managing patients with hematologic malignancies are presented in Table 115.4.

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CHAPTER 116 ■ ONCOLOGIC EMERGENCIES

DAMIAN J. GREEN, JOHN A. THOMPSON AND BRUCE MONTGOMERY

The clinical presentation of oncologic emergencies has not changed dramatically over the past 50 years; however, the efficacy and variety of therapeutic interventions have improved considerably. Because a patient's prognosis has a significant impact on the choice of treatments, it is of paramount importance for the intensivist and the care team to determine the following: (a) Is the clinical scenario truly emergent? (b) Is the syndrome related to malignancy, a side effect of treatment, or a benign process? (c) What is the specific tumor type that is responsible for the syndrome? (d) What is the stage of disease? (e) What studies are necessary to establish the diagnosis? (f) What are the wishes of the patient and family? The prognostic implications and the expected impact of treatment can then be weighed and appropriate therapy instituted or modified.

SUPERIOR VENA CAVA SYNDROME

Physiology

The superior vena cava (SVC) syndrome develops as a result of impaired blood return through the SVC to the right atrium. Obstruction results in venous hypertension, with the severity of ensuing signs and symptoms dependent on the site of obstruction and the rapidity with which the block occurs. The SVC is formed by the union of the left and right brachiocephalic veins in the middle third of the mediastinum and extends inferiorly

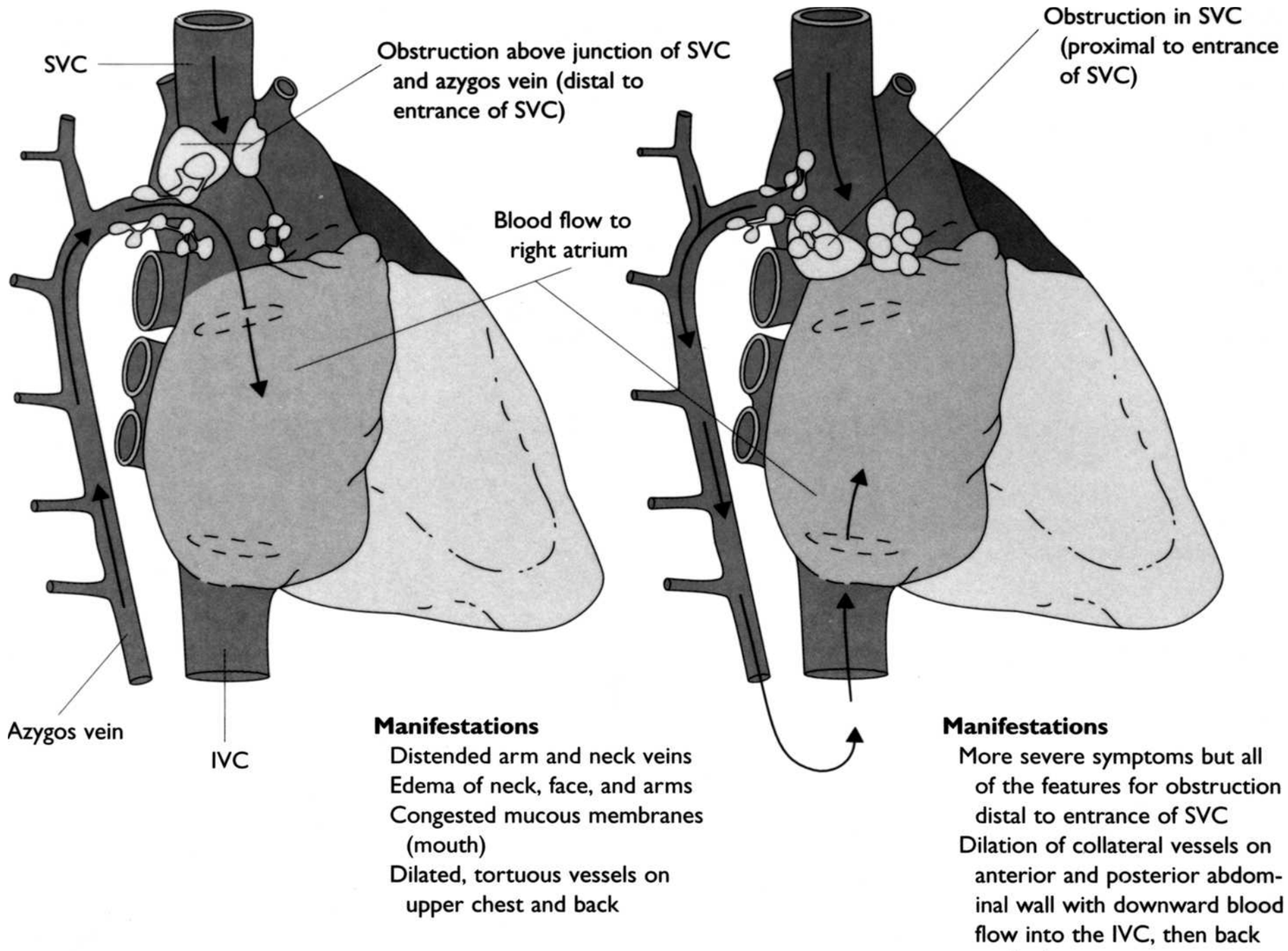


FIGURE 116.1. Anatomic locations of superior vena cava (SVC) obstruction leading to the SVC syndrome. IVC, inferior vena cava. [Reprinted from Skarin AT (ed): *Atlas of Diagnostic Oncology*. 2nd ed. St. Louis, Mosby, 1996, with permission.]

for 5 to 8 cm, terminating in the right atrium (Fig. 116.1). The SVC serves as the principal venous drainage for the head, neck, and upper extremities. The major collateral, the azygous vein, joins posteriorly just over the right mainstem bronchus and drains the posterior thorax. The SVC is thin walled and is bounded by the mediastinal parietal pleura and the right paratracheal, azygous, hilar, and subcarinal lymph nodes. As a result, it is extremely susceptible to extrinsic compression by adjacent lymph nodes or the aorta, with subsequent stasis, occlusion, or thrombosis. If obstruction occurs distal to the azygous vein, collateral flow through the azygous can adequately compensate for diminished return. However, if the obstruction is proximal to the azygous, flow must completely bypass the SVC and return via internal mammary, superficial thoracoabdominal, and vertebral venous systems to the inferior vena cava. This more circuitous route results in significantly higher venous pressures. The trachea and bronchi of children are smaller and significantly more susceptible to extrinsic compression, increasing the risk of fatal complications.

Etiology

The vast majority of patients with SVC syndrome have bronchogenic carcinoma, most commonly of the small cell histology (Table 116.1). Non-Hodgkin lymphoma, breast cancer, and other neoplasms make up the remainder of the malignant causes. Despite a high frequency of mediastinal involvement, Hodgkin lymphoma patients rarely present with SVC compression. Benign causes of SVC syndrome make up 6% to 20% of all cases and include thrombosis due to indwelling intravenous catheters or pacemakers and granulomatous disease [1,2]. Infectious causes of the SVC syndrome decreased substantially with the advent of antibiotics but must be considered in the differential diagnosis for patients from endemic areas or with potential human immunodeficiency virus infection. Blastomycosis, actinomycosis, histoplasmosis, tuberculosis, nocardia, and syphilis occasionally cause fibrosing mediastinitis and aortitis leading to SVC syndrome. An extensive list of rare causes may include idiopathic mediastinal fibrosis, goiter, thymoma, Behçet's syndrome, sarcoidosis, prior radiation with local vascular fibrosis, and unusual metastases of common malignancies.

Clinical Manifestations

The presentation of SVC syndrome depends largely on the acuity of the obstruction to flow. In patients with benign causes, extensive collateral flow often develops that minimizes symptoms

TABLE 116.1

PRIMARY DIAGNOSIS IN 125 CASES OF SVC SYNDROME

Histology	% of Cases	Total (%)
Lung carcinoma		79
Small cell	34	
Squamous cell	21	
Adenocarcinoma	14	
Large cell/other	11	
Lymphoma		14
Non-Hodgkin's lymphoma	13	
Hodgkin's lymphoma	0.8	
Other malignancy		6
Adenocarcinoma	3	
Kaposi's sarcoma	0.8	
Seminoma	0.8	
Acute myelomonocytic leukemia	0.8	
Leiomyosarcoma	0.8	

From Armstrong BA, Perez CA, Simpson JR, et al: Role of irradiation in the management of superior vena cava syndrome. *Int J Radiat Oncol Biol Phys* 13:531–539, 1987.

for months to years. Acute compression by tumor or thrombosis does not allow time for collateralization, and venous hypertension inevitably induces symptoms. Symptoms include dyspnea, edema of the face, neck, upper torso, and extremities; and cough. In rare instances, patients complain of hoarseness, syncope, headaches, chest pain, or dysphagia due to esophageal compression. Physical signs include jugular venous distention, edema of the face or upper extremities, dilated venous collaterals, plethora, and tachypnea and, in rare instances, papilledema or stridor.

Diagnosis

Initial evaluation should include a chest radiograph and contrast enhanced computed tomography (CT) to confirm the clinical diagnosis, identify a potential etiology, and localize the obstruction. Venography or magnetic resonance imaging (MRI) may be appropriate in subsequent evaluation to better define the extent of obstruction, particularly if stenting of the obstruction is considered (Fig. 116.2). Of note, focal hepatic contrast enhancement on CT has been noted in patients with SVC syndrome due to collateralization through patent remnants of the umbilical vein or of the musculophrenic venous system [3]. These abnormalities could be mistaken for metastatic disease and should be further evaluated in patients in whom therapy would be changed in the presence of isolated metastases. If a malignant cause of SVC obstruction is considered, all reasonable efforts should be made to obtain diagnostic material, as treatment depends on the underlying histology. The approach may include sputum cytology, bronchoscopy, transthoracic needle aspiration, biopsy of palpable lymph nodes, mediastinoscopy, thoracotomy, or video-assisted thoracoscopy. Despite concerns regarding surgical complications, morbidity associated with surgical procedures necessary to procure a diagnosis is not substantially different from that in patients without SVC syndrome [1,4]. The rapidity of the diagnostic workup depends on the likelihood of morbid complications at the time of presentation. Most series suggest that patients with malignant SVC syndrome have had symptoms an average of 45 days before presentation, and the vast majority of patients with malignancy do not die of SVC syndrome but of other complications of their disease [1]. The significant complications of SVC syndrome are tracheal obstruction and cerebral edema, and fatalities from cerebral edema are extremely rare. Therefore, the truly emergent situation in adults is a patient who presents with stridor or other evidence of significant airway compromise or the rare patient with cerebral edema. In essentially all other settings, treatment should be instituted only after the malignant or benign cause of the syndrome has been established because outcome is not compromised by delay for appropriate evaluation.

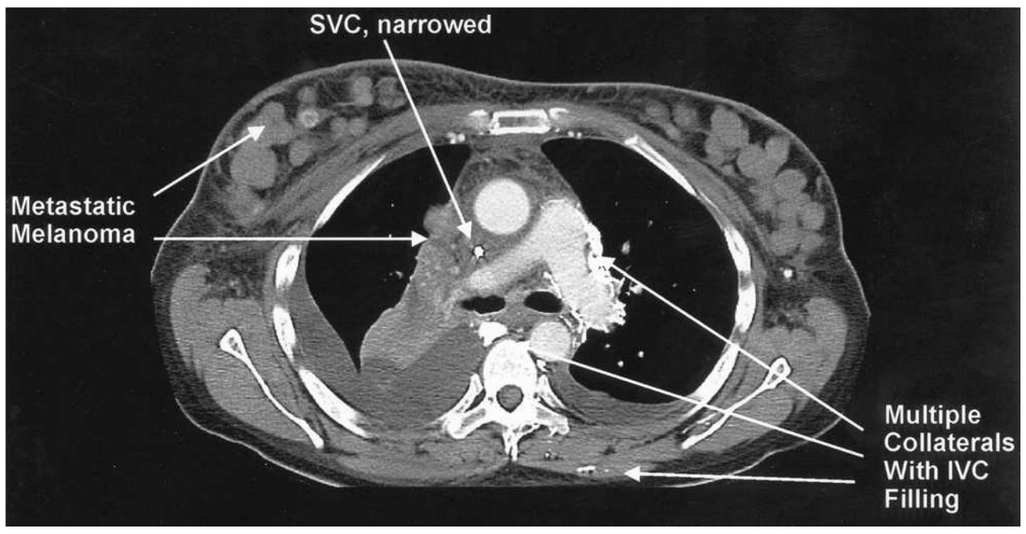


FIGURE 116.2. Upper extremity contrast injection demonstrating severe narrowing of the superior vena cava (SVC) with the development of multiple collaterals and inferior vena cava (IVC) filling.

Treatment

Once the diagnosis is established, initiation of therapy depends on the etiology, the severity of symptoms, the acuity of presentation, and the goals of treatment. If patients are minimally symptomatic, the azygous is patent, and treatment is focused on palliation, observation is a reasonable option. Chemotherapy is the treatment of choice for SVC syndrome due to small cell lung carcinoma, non-Hodgkin lymphoma, and germ cell tumors. Although radiation is often considered in addition to chemotherapy even in the palliative setting, 80% of these patients have a complete or partial response of their symptoms to chemotherapy alone [5]. Other histologies should be treated with endovascular stent placement, radiation therapy, or both. Radiation therapy prior to biopsy has been associated with a significant reduction in rates of histologic diagnosis and should be avoided [6]. Although external beam radiation effectively palliates symptoms in more than 70% of patients within 2 weeks [7], relapse after radiotherapy occurs in 15% to 30% of cases.

Endovascular stent placement, as a primary intervention, is a particularly attractive option for patients who lack a tissue diagnosis and whose symptoms on presentation require a rapid palliative intervention; including all patients, regardless of histology, who present with airway compromise or cerebral edema. In these patients, SVC stent placement provides rapid relief of symptoms (less than 48 hours) while awaiting response to systemic chemotherapy or radiation treatment. Responses to endovascular stent placement are durable (90% symptom free at time of death, versus 12% with palliative radiation) and the primary patency rates for malignant SVC syndrome are 50% to 100% [8]. Some authors have suggested a role for stent placement in first-line management of all SVC syndrome patients; however, no randomized controlled trials have been published [8].

Anticoagulation after stent placement is controversial, with some studies suggesting a high rate of thrombosis unless patients are anticoagulated, whereas other series, using no anticoagulation, report efficacy and thrombotic risk equivalent to those who use anticoagulation [9,10].

In patients with an established diagnosis, radiation therapy remains an appropriate intervention. Many fractionation protocols have been used, with the majority of patients receiving 30 Gy in 10 fractions, whereas patients treated with curative intent often receive 50 Gy in 25 fractions. Although high doses of radiation have often been given early in the treatment course to achieve rapid tumor response, there is little evidence to suggest that this is necessary [11]. In cases of SVC thrombosis with an indwelling catheter or pacemaker, thrombolytic agents may be useful as primary therapy or as an adjunct to stent placement [12]. The additional benefit of thrombolytics or anticoagulation in patients treated for malignant SVC syndrome is not well established.

Surgical resection and reconstruction of the SVC is reserved for patients with benign disease or the rare patient with tracheal obstruction in the setting of chemotherapy or radiotherapy-resistant disease.

SVC syndrome has been thought to predict for poor outcome. However, the presence of SVC syndrome is not a negative prognostic factor in small cell carcinoma and lymphoma independent of the stage and bulk of disease, and patients should be treated with curative intent if otherwise appropriate [13].

CARDIAC TAMPONADE

Physiology

Cardiac tamponade results from accumulation of fluid within the pericardium that impairs left ventricular expansion and diastolic filling. As stroke volume drops, compensatory tachycardia occurs to offset progressive hypotension. Ultimately, pressures equalize in the left atrium, pulmonary vasculature, right atrium, and SVC, and circulatory collapse ensues. As with SVC syndrome, the severity of symptoms is dependent on the speed of progression. Tamponade occurs when the pericardium cannot expand because fluid accumulation is too rapid or because the pericardium is thickened or fibrotic.

Etiology

Pericardial or cardiac involvement with malignancy occurs in 1% to 20% of patients with cancer and is often not diagnosed antemortem [14,15]. In up to 40% of unselected patients presenting with tamponade, malignancy is identified as the cause; the frequency with which tamponade develops as the initial manifestation of a patient's disease has led to standard cytologic examination of all significant effusions [16]. Tumors may involve the pericardium by direct extension from intrathoracic organs or hematogenous spread. Malignancies most often associated with pericardial effusions are lung, breast, lymphoma, and leukemia. Pericardial effusions in patients with cancer are due to pericardial or cardiac involvement in 60% of cases, with idiopathic pericarditis and radiation-induced pericarditis causing 32% and 10% of cases, respectively [17]. Other potential causes include infection, Dressler's syndrome, rheumatic disease, and hypothyroidism.

Clinical Manifestations

The common symptoms of pericardial effusion include dyspnea (85%), cough (30%), orthopnea (25%), and chest pain (20%). The common signs of pericardial effusion are jugular venous distention (100%), tachycardia (100%), pulsus paradoxus (89%), systolic blood pressure of less than 90 (52%), and pericardial rub (22%) [16]. Other signs of right- and left-sided heart failure may include hepatosplenomegaly, rales, peripheral edema, and ascites. Plain films demonstrate cardiac enlargement in at least half of all cases, and electrocardiography may reveal abnormalities suggestive of pericarditis (low-voltage, ST-segment elevation) or electrical alternans.

Diagnosis

Echocardiography is the most useful means of rapidly detecting hemodynamically significant effusions. Early signs include right atrial collapse and mitral regurgitation with later detection of left atrial or right ventricular collapse. Echocardiography also allows estimation of the volume, fluidity, and contents of the effusion, although it is difficult to distinguish tumor, thrombus, or fibrinous material from one another. The specificity of echocardiography for hemodynamic compromise has been called into question, and in many centers right heart catheterization with demonstration of equalization of pressures is required to diagnose tamponade physiology definitively. Emergent treatment of tamponade invariably involves drainage of the effusion, and cytologic evaluation of the fluid provides a very specific means of establishing a malignant etiology. The detection rate of pericardial fluid cytology ranges from 50% to 100%, and certain histologies, such as lymphoma and mesothelioma, are more difficult to demonstrate in pericardial fluid [14,18,19]. Pericardial biopsy is occasionally required to establish a diagnosis in difficult cases and can be performed under local anesthesia using a subxiphoid approach. The presence of a pericardial effusion correlates with a shortened survival among patients with cancer (median survival 15.1 weeks) and the definitive identification of neoplastic cells in the pericardial fluid by cytology portends an even worse prognosis (median survival 7.3 weeks) [20].

Treatment

Cardiac tamponade requires immediate treatment to relieve the increased end-diastolic pressure and inadequate ventricular filling. Oxygen, pressor agents, and intravenous fluids to improve cardiac output should be provided as appropriate. Inotropic agents are frequently ineffective however, because a state of intense adrenergic stimulation is already present [21]. When airway management is required, significant caution should be used because the positive intrathoracic pressure that results from initiation of mechanical ventilation places tamponade patients at particularly high risk for profound postintubation hypotension [21]. Emergent pericardiocentesis is indicated for significant hypotension, and it has been suggested that a pulse pressure of less than 20 mm Hg, a paradoxic pulse greater than 50% of the pulse pressure, or a peripheral venous pressure above 13 mm are other absolute indications for emergent intervention [22]. Fluid should be evaluated with cell counts, cultures, and cytology as noted earlier. Patients who present with malignant tamponade have recurrence after simple pericardiocentesis in 58% to 83% of cases [16,23]. Pericardial effusions without clinical tamponade may be observed if patients are asymptomatic or have minimal effusion (less than 1 cm), as progression to tamponade requiring pericardiocentesis in a single study was 20% for all patients, and progression of effusions of less than 1 cm in size to greater than 1 cm was only 4% [23]. Because of the high recurrence rate after pericardiocentesis in patients with tamponade, additional therapy is generally indicated if the patient's survival or quality of life would be otherwise compromised. Symptomatic relief with pericardiocentesis alone is 90% to 100%, with a complication rate of 3% [24]. Radiation therapy is noninvasive and allows treatment of the majority of the pericardium but carries a theoretical risk of radiation-induced pericarditis. As a single modality, radiation controls pericardial effusion in 67% of cases, with a particularly high success in hematopoietic tumors (93%). Systemic therapy is generally used only for diseases that are considered to be chemosensitive, such as breast cancer or lymphoma; in these individuals, it prevents recurrence in 73% of treated patients.

Instillation of sclerosing agents, radionuclides, and chemotherapy through indwelling catheters have been widely used with the intent to induce nonspecific inflammation with obliteration of the pericardial space or to achieve specific antineoplastic effects. Typically, a catheter is placed into the pericardial sac and drainage continued until output is less than 100 mL per day. Sclerosing agent or chemotherapy is injected into the catheter every 24 to 48 hours until fluid output is less than 25 to 50 mL per day, and the catheter is removed. A review of 20 different studies reported an overall control rate of 82% with common toxicities, including fever, pain, arrhythmias, and occasional cytopenias [24]. Tetracycline, which is no longer available, has the most extensive track record; however, doxycycline and minocycline have shown similar efficacy in malignant pericardial and pleural effusions. Chemotherapeutic agents that demonstrate response rates greater than 50%

include bleomycin, cisplatin, carboplatin, mitoxantrone, fluorouracil, and thiotepa [24–29]. In a randomized trial of 80 patients comparing intrapericardial bleomycin with observation alone following drainage, the 2-month failure free survival was 46% versus 29%; and median survival was 119 days versus 79 days for the groups, respectively. Because of the small size of this trial, these differences did not achieve statistical significance [30].

One small prospective trial ($n = 21$) comparing bleomycin with doxycycline showed bleomycin to be better tolerated, with less retrosternal pain and shorter periods of catheter drainage [28]. The use of sclerosing agents in the treatment of recurrent malignant pericardial effusions may result in an increased risk of both subsequent constrictive pericarditis and tamponade, leading some groups to favor the instillation of nonsclerosing chemotherapeutic agents [31]. In the absence of randomized studies, no single agent is accepted as the gold standard for intervention.

A surgical procedure or balloon catheter can be used to create a pericardial window to drain the fluid. This can be done by performing a subxiphoid pericardiotomy, thoracotomy or thoracoscopy with window, pleuroperitoneal window, or subcutaneous balloon pericardiotomy. These procedures control the effusion in 85% to 95% of patients [24,32–34]. An advantage of subxiphoid or balloon pericardiotomy is that both can be performed without general anesthesia, reducing operative morbidity.

Prognosis

The development of malignant pericardial effusion and tamponade usually reflects uncontrolled metastatic disease and portends a dire prognosis. Median survivals for patients treated for tamponade range from 3.3 to 4.5 months. Nonrandomized studies suggest that patients with lung and breast cancer have substantially better survival rates if systemic therapy can be instituted [35,36]. The decision to intervene in a patient with malignant cardiac tamponade depends on the patient's histology and sensitivity to treatment as well as the patient's condition. Patients for whom treatment of tamponade provides meaningful palliative benefit should be considered for the treatment that is likely to provide durable relief of symptoms with the minimum of morbidity and requirement for hospitalization.

MALIGNANT EPIDURAL CORD COMPRESSION

Few complications of malignancy are more dreaded than epidural cord compression. The associated pain, neurologic deficits, and dramatically impaired quality of life are serious problems for the patients who develop this condition and by extension for their families. Early recognition of the signs and symptoms of cord compression may prevent serious compromise in survival and functional capacity. *Epidural cord compression* is defined by compression of the dural sac and its contents by an extradural tumor mass. Minimum radiologic evidence for compression is indentation of the theca at the level of clinical features, which include pain, weakness, sensory disturbance, or evidence of sphincter dysfunction [37].

Physiology

Epidural cord compression by malignancy occurs as a result of metastasis or primary tumor involvement of the vertebral column, paravertebral space, or epidural space. Damage to the cord occurs when the tumor compromises the vertebral venous plexus or compresses neural tissue directly or when compromised bone impinges on the cord. The resulting vasogenic edema and hemorrhage induce further ischemic damage. The vertebral body is the most common source of compressive lesions, predominantly in the thoracic (70%), followed by the lumbar (20%) and cervical (10%) regions [38]. Tumor invasion through the intervertebral foramen and cord compression without bone involvement is most often seen with lymphoma, leading to normal plain films and radionuclide scans despite clinical compression. Multiple noncontiguous levels are involved in 10% to 40% of cases [39,40].

TABLE 116.2

PRIMARY DIAGNOSIS CAUSING EPIDURAL CORD COMPRESSION (N = 896)

Histology	% of Cases
Lung	18
Breast	13
Unknown primary	11
Lymphoma	10
Myeloma	8
Sarcoma	8
Prostate	6
Gastrointestinal tract	4
Renal	5
Other	17

Data from Weissman DE, Gilbert M, Wang H, et al: The use of computed tomography of the spine to identify patients at high risk for epidural metastases. *J Clin Oncol* 3:1541–1544, 1985; Ruff RL, Lanska DJ: Epidural metastases in prospectively evaluated veterans with cancer and back pain. *Cancer* 63:2234–2241, 1989.

Etiology

The most common causes of malignant cord compression are tumors with a propensity for bony metastases, including breast and lung, followed by hematopoietic malignancy and gastrointestinal and genitourinary primaries [41,42] (Table 116.2). Cord compression afflicts 5% of patients during their course and is found in up to 10% of patients at autopsy. Benign causes of cord compression include stenosis, epidural abscess, or hematoma.

Clinical Manifestations

The cardinal sign of malignant cord compression is pain, present in 95% of patients at diagnosis. Weakness, autonomic dysfunction, and sensory changes are present in more than 50% of cases [43]. The pain is typically worse with recumbency, coughing, straining, or exercise. Radicular pain develops later and is an important localizing sign. Weakness, sensory loss, and incontinence are also late findings. Urinary retention alone is very rarely a presentation of cord compression. Duration of symptoms before severe cord compression and paralysis is remarkably variable, ranging from years to 24 to 48 hours.

Diagnosis

The diagnosis of cord compression relies primarily on MRI, given its sensitivity, speed, and the ability to detect compression at multiple levels. The utility of radionuclide studies and radiographs for predicting cord compression is dependent entirely

on the patient's disease status (known vs. initial diagnosis of malignancy), symptoms, and neurologic examination [44]. In fact, at least 20% of patients with malignancy, back pain, and cord compression have neither localizing neurologic signs nor abnormal radiographs and would be misdiagnosed without further imaging studies [44]. MRI allows evaluation of the entire neuraxis, is more sensitive for detection of paraspinal disease, and may demonstrate leptomeningeal and intramedullary disease. Because the risk of malignant cord compression at the site of plain film abnormalities in a symptomatic patient with malignancy is so high, it has been proposed to bypass MRI and to radiate the cord two segments above and below the defined lesion [41]. However, a prospective study analyzed the expected outcome with that approach compared with treatment planning on the basis of MRI and found that MRI changed the radiotherapy plan in 53% of patients [45]. These changes included 21% of patients in whom all paraspinal disease would not have been treated and 5% of those in whom additional levels of true cord compression would not have been treated. In 30% of patients, the demonstrated level of compression on MRI was more than two vertebral levels away from the level indicated by neurologic examination. If patients are unable to undergo MRI because of claustrophobia, the presence of metal implants, or access, myelography can be performed instead. CT scanning is superior to MRI for definition of vertebral body anatomy and may be useful before consideration of surgical intervention.

Treatment

Therapeutic options include corticosteroids, surgery, and radiation. In emergent situations, corticosteroids are generally given while awaiting MRI to decrease peritumoral edema and to prevent edema formation during radiation. On the basis of laboratory studies and a single randomized controlled trial that compared high-dose dexamethasone with radiation to radiation alone [46], some authors support the use of high-dose dexamethasone, defined as a 100-mg intravenous bolus followed by 96 mg per day tapered over a 2-week period. This approach is efficacious, but adverse side effects are reported in up to 30% of patients [47]. Alternatively, a more standard approach is 10 mg intravenously followed by 4 mg every 6 hours tapered over 2 weeks, especially in patients who are clinically stable. Ambulatory patients without progressive deficit may forgo steroids altogether during radiotherapy without undue risk [48]. Historically, radiation therapy and direct decompressive surgery were felt to be equally effective as initial interventions in patients with metastatic spinal cord compression. A recent randomized trial comparing direct decompressive surgery plus postoperative radiotherapy to radiotherapy alone revealed a statistically significant outcome benefit to the combined approach under certain conditions. Compared with patients who received radiotherapy alone, more patients who underwent surgery were able to walk after treatment (84% vs. 57%) and were ambulatory for a significantly longer duration (median: 122 days, versus 13 days) [49]. A secondary data analysis from this randomized trial revealed no benefit from surgical intervention for patients greater than 65 years of age [50]. First-line radiation therapy remains an important option for patients who are known to have highly radiosensitive tumors; nonsurgical candidates; patients with multiple areas of spinal cord compression; and those who experienced symptoms of total paraplegia for longer than 48 hours at presentation. Because surgical complication rates approach 20% [51], radiation therapy should generally be used as the first-line intervention in patients over age 65. Specific radiation treatment plans for cord compression vary between centers. The most common course is 30 Gy in 10 fractions over 2 weeks.

TABLE 116.3

INCIDENCE OF HYPERCALCEMIA IN ADVANCED MALIGNANCY

Histology	% Who develop hypercalcemia
Breast	19–30
Lung	10–35
Multiple myeloma	20–30
Head and neck	5–24
Renal	17

Prognosis

Early intervention is vital to preserving function. For patients who are ambulatory at the time of treatment, at least 80% remain ambulatory. The development of paraparesis decreases the ambulation rate to 50%, and patients who are paraplegic at the time of therapy recover ambulation only 10% to 19% of the time after radiation therapy alone [37,43,49,52–55]. In paraplegic patients, outcomes appeared to be better for individuals who were candidates for upfront surgical decompression (62% of patients randomized to combined surgery plus radiation regained the ability to walk compared with 19% of those who received radiation alone), the difference was statistically significant, but the sample size was small ($n = 32$) [49].

HYPERCALCEMIA

Hypercalcemia of malignancy (HCM) is the most common emergent metabolic disorder associated with cancer, affecting 10% to 20% of patients with malignancy at some time during their clinical course (Table 116.3). Diagnosis and timely interventions are life saving in the short term but also enhance patients' compliance with primary and supportive treatments and may improve quality of life.

Physiology

In healthy persons, vitamin D and parathyroid hormone (PTH) control absorption and mobilization of calcium. Calcitriol, the active form of vitamin D, enhances gastrointestinal absorption and mobilizes calcium from bone. PTH increases renal calcium resorption in the distal tubule and also mobilizes calcium from bone. In patients with HCM, increased calcium mobilization combines with renal insufficiency to cause symptomatic hypercalcemia. At least two mechanisms are proposed: direct osteolysis by tumor or increased osteoclastic resorption as a result of humoral mediators. Both mechanisms may be active in many patients. The parathyroid hormone-related protein (PTHrP) is postulated to play a role in the majority of patients with HCM, as levels are elevated in at least 80% of cases [56]. PTHrP is a 139 amino acid protein that may give rise to several peptides with differing biologic activities [57,58]. PTHrP appears to have important roles in calcium transport and developmental biology, and the N-terminal 13 amino acids share amino acid sequence and homology with intact PTH. PTHrP stimulates osteoblasts to produce receptor activator of nuclear factor-κB ligand (RANKL) which in turn activates osteoclast precursors and leads to both osteolysis and the release of bone-derived growth factors. These growth factors, including transforming growth factor-β and insulin like growth factor-1, are known to both promote tumor cell proliferation and further increase production of PTHrP, which then continues to drive renal

calcium reabsorption [59]. Circulating vitamin D metabolites may be increased in some lymphomas, enhancing intestinal calcium absorption and causing or exacerbating hypercalcemia [60].

Normal kidneys are capable of filtering and excreting four to five times the normal calcium concentration in the serum to maintain serum calcium homeostasis. PTHrP increases renal tubular resorption and osteolytic calcium release, causing rapid and persistent elevation of extracellular calcium. The subsequent calciuria and osmotic diuresis result in volume depletion. Decreased glomerular filtration limits the kidney's ability to filter and excrete calcium, and proximal tubular calcium and sodium reabsorption increase, leading to further increases in serum calcium concentrations.

Symptoms of nausea and vomiting worsen the dehydration. If the concentration of calcium in the glomerular filtrate exceeds its solubility, calcium may precipitate in the renal tubules, further compromising renal function.

Etiology

HCM occurs most frequently in patients with breast cancer, multiple myeloma, and squamous cell malignancies of the lung, head and neck, and esophagus (Table 116.3). For instance, the incidence of hypercalcemia in patients with metastatic breast carcinoma is 20% to 30% [61,62]. A tumor "flare" can develop in patients with breast cancer after initiation of hormonal therapy, with associated pain and hypercalcemia, and this response may predict for better response to treatment [63]. Hypercalcemia develops in patients with metastatic lung carcinoma in 10% to 35% of cases but, almost invariably in non–small cell rather than small cell histology [64,65]. The development of hypercalcemia in patients with lung carcinoma in several series suggested that disease was unresectable and prognosis uniformly poor [66]. Some malignancies are rarely associated with hypercalcemia despite a propensity for widespread metastases, including prostate cancer and small cell lung cancer. Multiple myeloma commonly causes hypercalcemia, and up to 20% of myeloma patients may present with this complication. It represents advanced disease and, although associated with a worse prognosis, survival is substantially better than for patients with hypercalcemia resulting from solid tumors [67].

Clinical Manifestations

As with other oncologic emergencies, the rapidity with which hypercalcemia develops often determines the severity of symptoms. Patients may have significant symptoms with minimally elevated calcium and require therapy, whereas other patients are minimally symptomatic despite long-standing hypercalcemia. Many of the symptoms of hypercalcemia are relatively nonspecific, and the possibility of hypercalcemia must be kept in mind when considering patients with nausea, fatigue, lethargy, and mental status changes. Decreased intravascular volume and hypercalcemia cause malaise, fatigue, anorexia, and polyuria. Hypercalcemia decreases neuromuscular excitability and decreased muscle tone. Neuromuscular symptoms include weakness and diminished deep tendon reflexes. Neuropsychiatric manifestations may include confusion, lethargy, psychosis, or even coma. Hypercalcemia heightens cardiac contractility and irritability, and this is reflected by electrocardiographic changes, such as prolonged PR interval, widened QRS complex, and a shortened QT. With progressive hypercalcemia, bradyarrhythmias and bundle-branch block may develop, which can evolve to complete heart block and asystole.

Diagnosis

The diagnosis of hypercalcemia is documented by the presence of elevated corrected serum calcium, defined by the following formula: [4.0 − patient (Alb)] × 0.8 + [Ca], where Alb signifies albumin. Alternatively, an elevation of serum ionized calcium documents hypercalcemia and does not require the concomitant measurement of serum albumin. Other laboratory studies that should be considered include PTH, PTHrP, blood urea nitrogen and creatinine, phosphate, and magnesium. The assessment of a patient presenting with hypercalcemia should include several important aspects of disease history. Although hypercalcemia is a common complication of malignancy, other nonmalignant causes (including hyperparathyroidism, intravenous fluids, total parenteral nutrition, milk-alkali syndrome, thiazide diuretics, vitamins A and D, and lithium) are present in 10% to 15% of cancer patients who present with hypercalcemia and should be considered in the differential diagnosis.

Treatment

The decision to treat hypercalcemia should be dictated by the patient's history, current disease status, quality of life, and the wishes of the patient and family. The prognosis for most patients with HCM is poor. Severe pain, obstruction, or irreversible structural symptoms may be an indication not to pursue therapy. However, relief of the symptoms of hypercalcemia may improve quality of life and functional status for many patients during the remainder of their lifetimes. Patients who are symptomatic and who have no other potential etiology of hypercalcemia should be treated. If calcium is elevated but the patient is asymptomatic, specific hypocalcemic therapy can be held, with close observation, particularly if effective systemic therapy is to be initiated. Because most symptoms and the underlying physiology of hypercalcemia are due in part to volume depletion, intravenous hydration is the initial therapy of choice (Table 116.4). Although no randomized controlled clinical trials have been conducted to inform the approach to hydration, in general patients require repletion with 3 to 7 L intravenous saline over 24 to 36 hours to achieve euvolemia. If congestive heart failure is a concern or if the patient has severe hypercalcemia, loop diuretics can be used, but only after it is clear that adequate volume expansion has been achieved. If diuretics are used before the glomerular filtration rate has been restored, renal clearance of calcium is impaired further, and hypercalcemia may worsen despite the best intentions. Loop diuretics suppress

TABLE 116.4

ALGORITHM FOR CLINICAL MANAGEMENT OF HYPERCALCEMIA OF MALIGNANCY

Calcium Level	Symptoms	Therapy
< 12 mg/dL	None	Observation, or hydration followed by observation
< 12 mg/dL	Present	Hydration, bisphosphonate
12–14 mg/dL	Present	Hydration, bisphosphonate
> 14	Present	Hydration, bisphosphonate
> 14	Severe	Hydration, loop diuretics, calcitonin, bisphosphonate Alternatives: plicamycin, gallium nitrate, prednisone phosphate, dialysis

proximal absorption of sodium and calcium, augmenting calciuresis.

Bisphosphonates are the most useful hypocalcemic agents available for controlling HCM. They inhibit prenylation of small guanosine triphosphatases, which are necessary for osteoclast function and are cytotoxic to osteoclasts through a number of different mechanisms [68]. Zoledronic acid and pamidronate are the bisphosphonates currently in clinical use. Two randomized trials comparing pamidronate and zoledronic acid demonstrated improved response rates for zoledronic acid, 4- and 8-mg infusions; complete response rates by day 10 were 88.4%, 86.7%, and 69.7% for zoledronic acid, 4 mg and 8 mg, and pamidronate, 90 mg, respectively. Normalization of calcium occurred by day 4 in 50% of patients treated with zoledronic acid and 33% of those given pamidronate. Median duration of complete response favored zoledronic acid, 4 and 8 mg, over pamidronate, with response durations of 32, 43, and 18 days, respectively. Zoledronic acid is administered intravenously over 5 minutes. Optimal zoledronic acid dosage and administration schedules have not been established; the standard dose is 4 mg, with 8 mg reserved for patients with recurrent or refractory hypercalcemia. The onset of zoledronic acid's effect is apparent within 3 to 4 days, with maximal effect within 7 to 10 days, and lasts for 14 days to 2 months. Adverse effects include transient low-grade temperature elevations that typically occur within 24 to 36 hours after administration and persist for up to 2 days (≤20% of patients). Other bisphosphonates (except clodronate) may also produce transient fever, and the incidence of temperature elevation, nausea, anorexia, dyspepsia, and vomiting may be increased by rapid administration. New-onset hypophosphatemia and hypomagnesemia may occur; preexisting abnormalities in the same electrolytes may be exacerbated by treatment. Serum calcium may fall below the normal range, although symptoms are rare. Renal insufficiency has occurred in ongoing clinical trials at the 8-mg dose level and must be considered in patients with existing renal insufficiency [69]. No dose reduction is recommended for patients receiving the 4-mg dose of zoledronic acid when the measured serum creatinine is less than 3.0 mg per dL [70]. Another bisphosphonate, ibandronate, has demonstrated comparable activity and a longer duration of efficacy when compared to pamidronate in a randomized study of patients with hypercalcemia. Ibandronate appears to be the least nephrotoxic bisphosphonate agent, leading some authors to advocate its use in patients with renal impairment; however ibandronate is not currently approved for the management of hypercalcemia of malignancy by the Food and Drug Administration (FDA) in the United States [71]. An association has been reported between bisphosphonate therapy and subsequent development of osteonecrosis of the jaw.

The incidence is higher with zoledronic acid than with pamidronate (10% vs. 4%) and the risk is significantly increased in individuals with underlying dental conditions or those undergoing dental procedures during treatment. Patients on chronic therapy appear to be at greatest risk [72].

Other treatments for HCM include corticosteroids, calcitonin, plicamycin, and gallium nitrate. Calcitonin rapidly inhibits bone resorption and decreases renal calcium reabsorption. Salmon calcitonin is administered at 4 IU per kg subcutaneously or intramuscularly every 12 hours, and tachyphylaxis occurs rapidly, necessitating dosing increases to 8 IU every 6 to 12 hours. Efficacy is limited to the first 24 to 48 hours after initiation of therapy, and additional treatment with bisphosphonate should be considered concurrent with calcitonin. Corticosteroids are effective in lymphoma and multiple myeloma, tumors in which steroids are often cytotoxic. The onset of action is slow, over several weeks, and the mechanism of effect is through treatment of the underlying malignancy and suppression of gastrointestinal calcium absorption. Therapies designed to interfere with RANKL binding, including the monoclonal antibody denosumab and a decoy RANLK receptor, osteoprotegerin, appear to decrease serum calcium levels in preclinical and clinical settings, however no randomized clinical trials have been performed to evaluate these agents in patients with hypercalcemia [59,73–75]. Dialysis should be considered for patients with severe renal insufficiency and associated electrolyte abnormalities, particularly in patients for whom effective therapy is available.

Hypercalcemia reflects biologically aggressive, advanced disease. For patients with solid tumors, particularly those with chemotherapy-resistant disease, the prognosis is extremely grim, with median survivals of 30 to 60 days in most studies [76]. By contrast, hypercalcemia in patients with multiple myeloma and breast cancer is associated with relatively longer survival. The argument has been made that treatment of HCM prolongs survival in patients in whom other morbid complications of their disease will develop. In fact, it is clear that hypocalcemic agents do not prolong survival but can have impressive palliative benefit in relieving symptoms from hypercalcemia, such as nausea, emesis, and constipation, and improving pain control for some patients who achieve normocalcemia [76].

LEUKOSTASIS

Physiology

Leukostasis is a potentially devastating complication of leukemia in patients who present with hyperleukocytosis, defined as a leukocyte count greater than 100,000 per μL. The syndrome of leukostasis is related to obstruction of flow in capillary beds of the central nervous system, lungs, and heart by immature, rigid blasts. Although viscosity might be expected to play a role, it is rarely elevated because the principal determinant of viscosity, red blood cells, is often low due to marrow replacement by leukemic blasts. The obstruction of capillary beds by blasts and restricted flow results in tissue hypoxia, cytokine release, and coagulation. Tissue invasion also occurs and is not affected by leukapheresis. The risk of leukostasis was evaluated by Lichtman and Rowe [77], who demonstrated that the leukocrit, which is proportional to the number and volume of circulating leukocytes and blasts, was the parameter most closely associated with the development of leukostasis. Although integrins are postulated to play a role in the syndrome, analysis of vascular endothelium in patients with leukostasis compared with controls showed no significant differences in expression of vascular cellular adhesion molecule-1, endothelial–leukocyte adhesion molecule-1, or intercellular adhesion molecule-1 [78]. In vitro studies suggest that in the presence of inflammatory cytokines, leukemic blasts can adhere to vascular endothelium and that these blasts are capable of secreting multiple mediators of endothelial damage [79]. Until clinical correlations between cytokine excretion, integrin expression, and the development of leukostasis are available, the role of integrins in development of the syndrome will remain speculative.

Etiology

Hyperleukocytosis occurs in 10% to 20% of patients with acute myelogenous leukemia (AML) at presentation and is much less common in patients with chronic myelogenous leukemia, acute lymphoblastic leukemia, or chronic lymphocytic leukemia. For equivalent degrees of leukocytosis, the risk of leukostasis is much higher with AML than with other diagnoses because of the larger size and adhesion characteristics of

TABLE 116.5

ALGORITHM FOR TREATMENT OF SYMPTOMATIC HYPONATREMIA

Acute	Mildly symptomatic	Na < 125 mg/dL	Free water restriction 500–1,000 mL/d Demeclocycline Avoid in renal/hepatic dysfunction
Acute	Severe symptoms	Na < 115 mg/dL	3% saline Furosemide diuresis

AML blasts. The risk of developing leukostasis depends on total white blood cell count (WBC), the percentage of blasts, and the rate at which counts are rising. The clinical presentation, diagnosis, and management of hyperleukocytosis are discussed in further detail in Chapter 115.

HYPONATREMIA

Physiology

Clinically symptomatic hyponatremia is a relatively rare complication of malignancy affecting only 1% to 2% of cancer patients. In the majority of these individuals, the syndrome of inappropriate antidiuretic hormone (SIADH) develops. Secretion of ectopic ADH occurs almost solely in patients with small cell bronchogenic carcinoma, and the majority of other patients have coincident central nervous system or pulmonary disease. As a result of excess ADH, excessive water resorption occurs in the collecting ducts, and extracellular fluid osmolality decreases inappropriately. Water is able to move freely, and the decrease in extracellular osmolality results in a shift to the intracellular compartment with associated cellular edema. When hyponatremia occurs acutely, this edema causes dramatic neuronal edema and subsequent neurologic symptoms. Plasma volume expands, and urinary sodium excretion parallels the rate of oral sodium intake. Typically, the patient with SIADH is euvolemic to slightly hypervolemic, urine sodium is greater than 20 mEq per L, and plasma urea, uric acid, creatinine, and rennin activity are normal or low.

Etiology

At presentation, hyponatremia develops in more than 50% of patients with small cell carcinoma after free water loading, but symptoms develop in fewer than 10% of patients. SIADH has also been reported in a broad variety of other malignancies but is most commonly found in the setting of central nervous system or pulmonary metastases. SIADH may also develop in patients with malignancy due to other conditions, including the use of opiates, vinca alkaloids, β agonists, chlorpropamide, and cyclophosphamide. Hypoadrenalism due to rapid tapering of therapeutic corticosteroids is also a common etiology for mild hyponatremia. Other etiologies include volume contraction due to emesis or diarrhea, renal wasting due to diuretics or intrinsic renal disease, and pseudohyponatremia from excess serum lipids or paraproteins. Hypothyroidism and pulmonary or central nervous system disease are also potential causes of SIADH.

Diagnosis

Hyponatremia is often manifested as fatigue, nausea, myalgia, headaches, and subtle neurologic symptoms. Rapid drops in serum sodium or levels less than 115 mg per dL cause altered mental status, seizures, coma, pathologic reflexes, and papilledema. The diagnostic evaluation includes a review of medications and assessment of volume status as well as serum and urine electrolytes, osmolality, and creatinine. Patients with SIADH have inappropriately elevated urine sodium, and urine osmolality is greater than plasma osmolality but never reaches maximal dilution (less than 100 μOsm). Thyroid and adrenal dysfunction cause similar electrolyte imbalances and must be ruled out if laboratory studies suggest SIADH. CT or radiographs of the chest and brain may be necessary to eliminate pulmonary or central nervous system disease as causes of excessive ADH secretion.

Treatment

Treatment of the hyponatremia is tailored to the acuity with which it developed and the extent of symptoms that the patient is experiencing. Chronic severe hyponatremia should be treated with fluid restriction alone. Treatment of the underlying malignancy may alleviate SIADH due to small cell carcinoma. Local therapy to brain or pulmonary metastases may improve serum sodium, and discontinuing offending medications should be effective. Acute symptomatic hyponatremia can be treated as indicated in Table 116.5.

Free water restriction is expected to improve hyponatremia within 7 to 10 days. Demeclocycline induces a dose-dependent, reversible nephrogenic diabetes insipidus and is expected to correct sodium within 3 to 4 days. The primary side effect of demeclocycline is renal toxicity, and the risk of toxicity is increased by renal or hepatic dysfunction. The initial dose of demeclocycline is 600 mg daily to a maximum of 1,200 mg per day in two- to three-times-a-day dosing.

Patients who are seizing, comatose, or rapidly decompensating should be treated with hypertonic saline and furosemide to induce an isotonic diuresis as originally proposed by Gross et al. [80] and Hantman et al. [81]. Once the sodium level is above 120 mg per dL, more conservative measures are appropriate. The primary risk of rapid correction of hyponatremia is central pontine myelinolysis, which typically occurs 3 to 5 days after repletion with corticobulbar spinal dysfunction, dysphasia, quadriparesis, and delirium. Although controversial, most data support the idea that the risk of pontine myelinolysis is greatest for patients with chronic, severe hyponatremia who are treated too rapidly. Generally, the sodium level should not be corrected at a rate faster than 0.5 mM per L per hour even in acute circumstances [82].

TUMOR LYSIS SYNDROME

Physiology

Tumor lysis syndrome (TLS) is a metabolic emergency that remains a significant risk for patients with hematopoietic

malignancy and is being recognized with greater frequency in patients with solid tumors. TLS results from the release of intracellular purines, phosphate, and potassium from rapidly proliferating tumor cells, which may occur spontaneously or with the initiation of therapy. The massive tumor necrosis that initiates the syndrome may occur as a result of tumor hypoxia or with the use of chemotherapy, radiation, or embolization of tumor. Tumor lysis is followed by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and renal insufficiency. The hyperuricemia, combined with metabolic acidosis, results in crystallization of uric acid in the collecting ducts of the kidneys and ureters, leading to obstructive uropathy. Hyperphosphatemia may also cause metastatic calcification in the renal tubules. The resultant renal insufficiency worsens hyperkalemia and hypocalcemia.

Etiology

Patients at highest risk include those with lymphoma, particularly high-grade Burkitt's or non-Burkitt's non-Hodgkin's lymphoma and acute leukemia. The frequency of TLS depends on the criteria used, which are not well established or accepted. In Burkitt's lymphoma the incidence may be as high as 30%, and in patients with acute leukemia with hyperleukocytosis, electrolyte disturbances develop consistent with TLS in 50% of cases [83,84]. A variety of solid tumors have been reported to cause the syndrome, but the most common appear to be small cell lung carcinoma, breast carcinoma, and neuroblastoma. Others include ovarian and vulvar carcinoma, medulloblastoma, sarcomas, seminoma, and melanoma [85,86]. The pretreatment variables that predict the occurrence of the syndrome are azotemia and elevated lactic dehydrogenase and hyperuricemia, evidence of a rapidly proliferating tumor undergoing spontaneous necrosis. Generally, these malignancies are clinically aggressive and sensitive to chemotherapy or radiation.

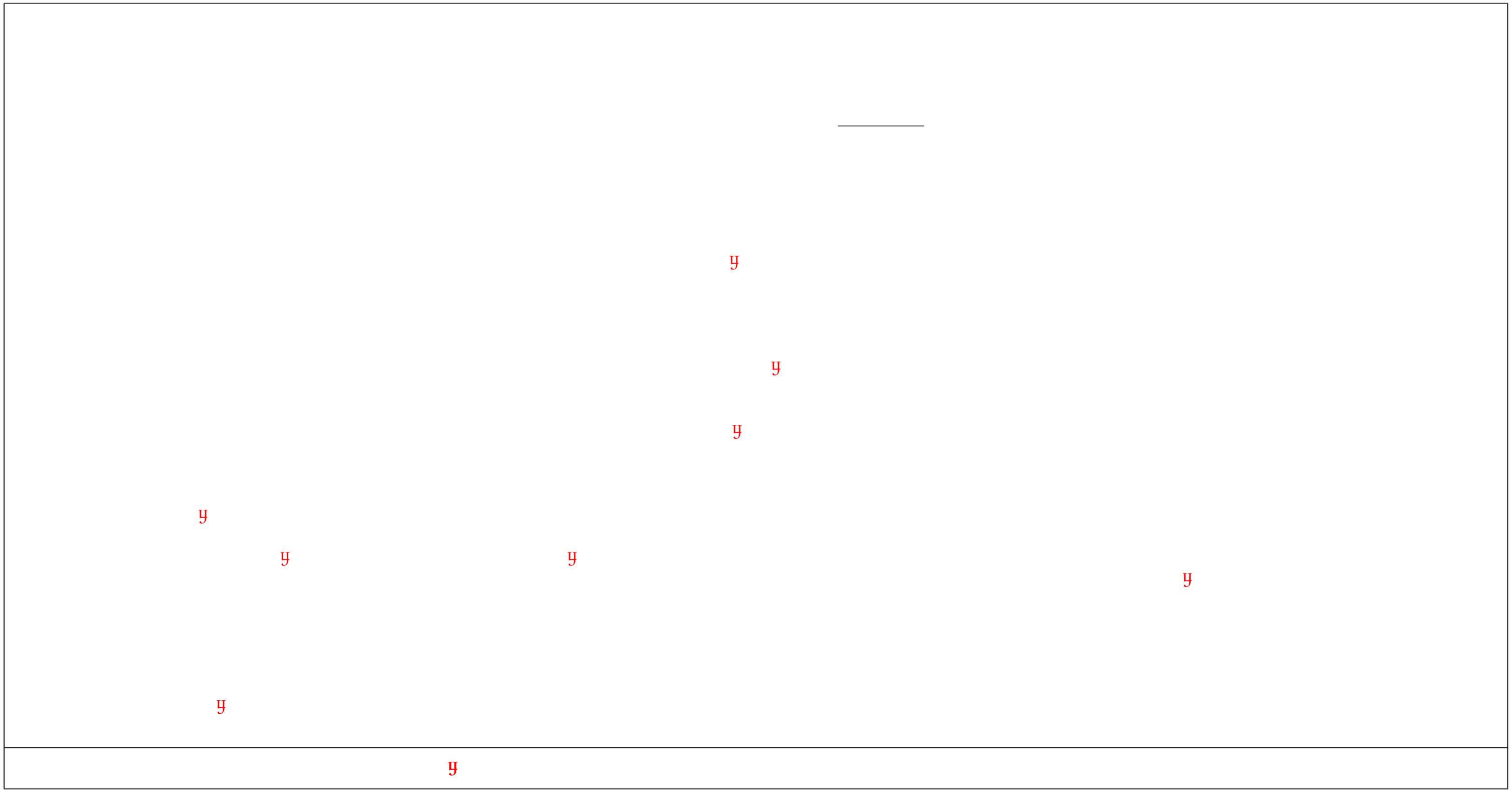
Diagnosis

The diagnosis of TLS is a clinical one, as there is no specific pathognomonic finding or laboratory value that is specific to the syndrome. The diagnosis of TLS is made on the basis of the presence of azotemia, hyperuricemia, hyperphosphatemia, and hypocalcemia in a patient with extensive, rapidly proliferating tumor. The incidence of hyperkalemia is somewhat more variable. Profound metabolic acidosis out of proportion to the degree of renal insufficiency is common. Many of the metabolic abnormalities of TLS may occur as a result of acute renal failure alone, and a urinary uric acid to creatinine ratio greater than 1 helps to distinguish acute uric acid nephropathy from other catabolic forms of acute renal failure in which serum urate is elevated.

Treatment

Management can be grouped into prevention/conservative therapy and hemodialysis. Allopurinol in doses of 200 to 600 mg per m^2 per day should be initiated before therapy to decrease uric acid production [87]. Intravenous allopurinol is safe and effective and is indicated for patients who are unable to take oral allopurinol because of being non per os (NPO) for surgery or having respiratory distress/intubation or abnormal gastrointestinal motility/absorption [88]. Intravenous hydration at 200 to 300 mL per hour containing 25 to 50 mEq per L $NaHCO_3$ should be given to expand volume, alkalinize the urine, and wash out the renal medulla. It is preferable to decrease urine osmolality to isotonic and to increase urinary pH to greater than 7.0. In practice this is sometimes difficult, and in our experience isotonic $NaHCO_3$ (1.4%) more effectively achieves alkaline urine, although the risk of fluid overload is somewhat greater. Increasing metastatic calcification with the development of alkalemia is also a risk; however, the incidence of this complication is far less than that of renal insufficiency related to deposition of insoluble uric acid. Hyperkalemia should be aggressively managed with potassium restriction and sodium polystyrene sulfonate as appropriate. Hemodialysis is often necessary and is indicated to control volume, reduce phosphorus and uric acid levels, and manage uremia. Some proposed criteria for initiation of hemodialysis are persistent hyperkalemia despite conventional treatment, rapidly rising phosphate, symptomatic hypocalcemia, fluid overload, severe metabolic acidosis, and hyperuricemia. Typically, daily dialysis is necessary because the catabolic rate is sharply increased in patients with TLS. Daily weights, close monitoring of fluid intake and output, and serum electrolytes, including potassium, calcium, phosphorus, and uric acid, should be performed at least twice a day in a patient at high risk and more frequently if dialysis is instituted. Allopurinol is associated with a significant number of side effects and should be discontinued within 3 days of completion of treatment if there is no evidence of tumor lysis. Rasburicase is a recombinant urate oxidase that converts uric acid to more soluble allantoin. A randomized study of rasburicase and allopurinol in pediatric patients at high risk of tumor lysis demonstrated that uric acid levels were substantially lower in patients receiving prophylactic rasburicase. The size of the trial was too small to demonstrate a significant difference in renal failure, and the incidence of tumor lysis was not reported [89]. Two compassionate-use rasburicase trials involving pediatric and adult cancer patients have documented impressive efficacy in both the prevention and treatment of hyperuricemia [90,91]. Rasburicase was approved by the U.S. FDA for the initial management of elevated plasma uric acid levels in 2009. Approval was based on findings from a postmarketing surveillance randomized multicenter trial (EFC 4978) which demonstrated a statistically significant difference in response rate (fraction of patients with a plasma uric acid levels <7.5 mg per dL) among rasburicase-treated leukemia, lymphoma, and solid tumor patients (87% response) when compared with patients treated with allopurinol (66%). Interestingly, although the serum uric acid was significantly lower in the rasburicase-treated group, there was no difference between the arms in incidence of TLS. Rasburicase was administered at a dose of 0.2 mg per kg per day for 5 days. The most common rasburicase-associated toxicities included edema (50%), vomiting (38%), hyperbilirubinemia (16%), and sepsis (12%) [92]. A subsequent randomized trial of 64 patients comparing rasburicase administered daily (0.15 mg per kg per day) for 5 days versus a single dose followed by "as needed" dosing in adult patients with hematologic malignancies at risk for developing tumor lysis syndrome. The single-dose group demonstrated a sustained response in 87% of patients demonstrating that it is reasonable to decrease the duration of administration and follow uric acid levels in selected patients [93]. When rasburicase is used, it is important to recognize that the enzyme can continue to degrade uric acid in blood samples at room temperature. Samples must be collected in prechilled heparinized tubes, transported on ice, and analyzed within 4 hours of collection. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.

Outcome with development of full-blown tumor lysis syndrome is variable. In the reported cases of solid tumor TLS, the fatality rate was very high (36%) [85]. Institution of prophylaxis in patients identified as high risk (even those with solid tumors), which includes both rasburicase and consideration



for early use of hemodialysis, are highly recommended. Some institutions initiate induction therapy with vincristine, oral cyclophosphamide, and corticosteroids for patients with high-grade lymphoma in an attempt to decrease tumor burden more slowly and avoid the metabolic effect of sudden lysis [94]. No reports to date quantify the effect of this intervention on the incidence of TLS.

Advances in oncologic emergencies, based on randomized, controlled trials or meta-analyses of such trials, are summarized in Table 116.6.

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LUKE YIP · KENNON HEARD · STEVEN B. BIRD

CHAPTER 117 ■ GENERAL CONSIDERATIONS IN THE EVALUATION AND TREATMENT OF POISONING

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The objective of this chapter is to provide the general intensivist with both an overview and an approach to the management of the critically ill poisoned patient. General concepts germane to the intensive care unit (ICU) will be introduced and explored. Every attempt has been made to be as evidence based as possible, within the intrinsic limitations of the medical toxicology literature.

Because overdose studies cannot ethically be performed in humans and animal data may not be available or applicable to humans, predicting the severity of poisoning must be based on toxicodynamic data from previously published reports of human poisonings. However, such data are often incomplete or altogether unavailable and are always limited by the accuracy of the overdose history.

Poisoning or *intoxication* is defined as the occurrence of harmful effects resulting from exposure to a foreign chemical or xenobiotic. Such effects may be local (i.e., limited to exposed body surfaces), subjective (i.e., symptoms only) or systemic and objective (e.g., behavioral, biochemical, cognitive, or physiologic). In the absence of signs or symptoms, external or internal body contact with a potentially harmful amount of a chemical is merely an exposure. An *overdose* is an excessive exposure to a chemical that in specified (e.g., therapeutic) amounts is normally intended for human use. Whether an exposure or overdose results in poisoning depends more on the conditions of exposure (primarily the dose) than the identity of the agent involved. Ordinarily safe chemicals, even those essential for life such as oxygen and water, in excessive amounts or by an inappropriate route can result in harmful effects. Conversely, by limiting the dose, chemicals usually thought of as poisons can be rendered harmless. Poisoning is distinguished from adverse allergic, intolerance, and idiosyncratic pharmacogenetic reactions in that effects are concentration or dose related and, hence, predictable. As such, it includes adverse drug reactions due to unwanted secondary effects and pharmacokinetic and pharmacodynamic interactions.

Poisonings, exposures, and overdoses may be characterized by the route, duration, and intent of exposure. Ingestion, dermal or ophthalmic contact, inhalation, and parenteral injection (including bites and stings) are the most common routes, but rectal, urethral, vaginal, bladder, peritoneal, intraocular, and intrathecal exposures can also occur. Events that occur once or during a short period of time are considered acute, whereas those that occur repeatedly or over a prolonged time interval are said to be chronic

EPIDEMIOLOGY

Although comprehensive data regarding the true incidence of poisoning are not available [1], it is clearly a significant medical problem. Just under two and a half million human exposures were reported to the National Poison Data System in 2007 [2]. Of these, 20% to 25% are treated at a health care facility, and approximately 6% are admitted to a hospital. Half of those admitted are treated in an ICU. In other countries, the ICU admission rate for those evaluated at a health care facility varies from 5% to 22% [3–5].

Exposures and poisonings are responsible for 1% to 5% of emergency department visits, 5% to 10% of all ambulance transports, 5% to 14% of adult ICU admissions, and 2% to 5% of pediatric hospital admissions [3–9]. In addition, 25% of routine medical admissions involve some form of drug-related adverse patient event (an adverse drug reaction or noncompliance), and up to 30% of acute psychiatric admissions are prompted by attempted self-harm via chemical exposure. Although the incidence of poisoning in children has decreased since the introduction of the Poison Prevention Packaging Act in 1970 [10], the overall incidence of poisoning is increasing, particularly that due to suicide attempts in teens, middle-aged adults, and the elderly. The volume of calls handled by United States Poison Centers increased by 7.6% in 2007 [2]. Poisoning is second only to firearms as the leading cause of suicide [5]. Poisoning is the second leading cause of injury death [2]. The yearly medical cost for the treatment of poisoning in the United States is estimated to be $26 billion [11]. Poisoning accounts for 6% of the economic costs of all injuries in the United States [11].

Most exposures reported to US poison centers are acute (90.9%), unintentional (83.2%), occur at home (92.9%), cause minor or no harmful effects (95%), result from ingestion (78.4%), and involve children 6 years of age or younger (51.2%) [2].

Poisoning accounts for 2% to 14% of all ICU admissions, with an average length of stay of about 3 days [3,5,7–9]. The mortality rate for such patients varies from 0.6% to 6.1% [3,4,6–9]. Although only 1,239 poisoning fatalities were reported by US poison centers in 2007 [2], death certificate data indicate that the true number of poisoning deaths is 20 to 50 times higher [12]. Poison center statistics vastly underestimate mortality from poisoning because they rarely capture cases in which the victim is found dead and goes directly to the medical examiner.

PHARMACOLOGIC CONCEPTS

Toxic exposures all undergo the same pharmacologic steps, as outlined in Table 117.1. Clinician familiarity with toxicokinetics is essential for predicting the effect of a particular exposure and guiding appropriate treatment and disposition. Only a

TABLE 117.1

TOXICOKINETIC STAGES

1. Absorption
2. Distribution
3. Metabolism
4. Excretion

brief overview of these concepts is presented here. The reader is referred to other sources for additional information [13–17]. Details regarding the disposition and toxic effects of specific agents can be found in subsequent chapters and other references [14–27].

Mechanism of Action

Most chemicals are absorbed and cause systemic poisoning by selectively binding to and disrupting the function of specific targets (e.g., enzymes, proteins, membrane lipids, or neurohumoral receptors). Effects may be systemic or limited to a specific organ or tissue, depending on the distribution and location of target site.

Poisoning is usually functional and reversible. Hence, if end organ function can be supported, complete patient recovery is possible upon toxin elimination. However, if normal activity of the target site is essential for cell viability, a toxic exposure may result in necrosis. Agents that can cause fatal cellular damage include acetaminophen, carbon monoxide, corrosives, toxic alcohols, heavy metals, and neurotoxic hydrocarbons.

Absorption

Absorption involves the translocation of chemicals across the membranes of cells that make up mucosal surfaces, pulmonary epithelium, and skin, all of which function as biologic barriers. Translocation occurs by filtration or passive diffusion through gaps or membrane pores by dissolving in and diffusing through the membrane itself (e.g., lipid-soluble chemicals), or by attaching to carrier molecules in the membrane, which actively or passively facilitate diffusion (e.g., water-soluble chemicals). The rate and extent of absorption depend on physical properties of the chemical and the route of exposure. In general, only chemicals that are small (i.e., <4 nm in diameter), have low molecular weight (i.e., <50 Da), and are soluble in both water and lipids at the pH of body fluids can readily cross membranes.

Absorption after intravenous injection is complete and almost instantaneous. Peak arterial and venous blood concentrations occur within 30 to 90 seconds. Most toxins cross biologic membranes by simple passive diffusion. The rate at which this occurs is governed by Fick's law of diffusion.

$$\text{Rate of Diffusion} = dQ/dt = [DAK(C1 - C2)]/d$$

where D is the diffusion constant (constant for each toxin), A is the membrane surface area, K is the partition coefficient (represents the lipid: water partitioning of the toxin), d is the membrane thickness, and C is the toxin concentration.

Pulmonary absorption is rapid but incomplete. Blood concentrations peak within seconds to minutes. The absorption of chemicals after intramuscular or subcutaneous injection is slower but relatively complete. Peak blood levels generally occur within an hour of administration. Poor water solubility (low K) is responsible for the slow absorption and long duration of action of intramuscular depot formulations (e.g., neuroleptics).

The rate and extent of absorption after ingestion are variable. Peak blood levels are typically noted within 0.5 to 2.0 hours of a therapeutic dose. The absorbed dose is proportional to, but not necessarily equal to, the administered dose. The rate and extent of absorption after contact with other mucosal surfaces (e.g., oral, nasal, ophthalmic, rectal) is similar to ingestion. Skin absorption, if it occurs at all, is usually considerably slower. Regardless of route, absorption tends to follow first-order kinetics (i.e., the amount of chemical absorbed per unit of time is directly proportional to its concentration). *Hence, threshold tissue concentrations are usually reached more quickly and effects begin sooner after an overdose than after a therapeutic dose.*

Zero-Order Kinetics: rate of reaction is not proportional to toxin concentration

First-Order Kinetics: rate of reaction is proportional to toxin concentration

The dissolution and solvation of particulate material is often a rate-limiting step in gastrointestinal (GI) drug absorption. Hence, pill, solid, and suppository formulations tend to be absorbed more slowly than liquids, powders, or suspensions. Slow dissolution and solvation also account for the delayed and prolonged absorption of enteric-coated tablets (e.g., aspirin, potassium), sustained-release preparations (e.g., cardiovascular drugs, lithium, phenytoin, theophylline), drugs that tend to form concretions (e.g., ethchlorvynol, glutethimide, heavy metals, iron, lithium, and meprobamate), and those with poor water solubility (e.g., carbamazepine and digoxin). The rate of dissolution is also inversely related to the tablet concentration. *Hence, absorption generally takes longer and peak effects occur later after an overdose than after a therapeutic one.*

Ingested chemicals are predominantly absorbed from the small intestine rather than the stomach because the small intestine has a larger surface area. Hence, decreased gastric emptying or bowel activity caused by the presence of food, disease, or the effects of ingested agents (e.g., anticholinergics, opioids, sedative–hypnotics, salicylates) can also delay or prolong absorption. Food and coingestants may decrease absorption by binding to the chemical within the gut lumen or by competitively inhibiting its dissolution and translocation. Absorption may also be decreased if intestinal motility is excessive.

Distribution

During distribution, chemicals may become bound to and inactivated by endogenous nontarget molecules such as serum proteins. The final distribution of chemical is uneven and reflects its affinity for active and inactive binding sites and the locations of such sites. It is also influenced by biologic variables such as age, sex, weight, and disease states as they relate to body composition (e.g., water, fat, muscle content) and serum protein concentrations. The extent of distribution of a chemical is reflected by its apparent volume of distribution, measured in liters per kilogram of body weight, and calculated most simply by dividing the amount of chemical in the body (i.e., the absorbed or bioavailable dose) by its plasma concentration.

$$\text{Volume of Distribution} = \text{Bioavailable Dose}/\text{Plasma Concentration}$$

Because distribution is also a translocation process, it is influenced by the same chemical characteristics as absorption and follows first-order kinetics. Distribution generally occurs much faster than absorption, as evidenced by the occurrence of peak effects within minutes of an IV drug injection. Slow distribution is partly responsible for the delayed onset of action of some agents (e.g., digitalis, heavy metals, lithium, and salicylates).

Tissue Concentration

The severity of poisoning reflects the concentration of a chemical at its site(s) of action and is proportional to the dose. Because the blood concentration of a chemical is also proportional to the dose, blood levels are sometimes used as a surrogate to assess the severity of poisoning. However, blood and target site concentrations are not always in steady-state equilibrium. When distribution occurs more slowly than absorption (e.g., after IV administration, inhalational exposure, and the ingestion of agents with inherently slow distribution), blood levels may be higher than those in tissue. Conversely, when redistribution of a chemical from tissue to blood occurs more slowly than elimination (e.g., after extracorporeal removal), blood levels may be lower than those in tissue. In both instances, blood levels do not accurately reflect those in tissue and do not correlate with the severity of poisoning.

Age, genetic influences, tolerance, underlying disease, and the presence or absence of other chemicals may have synergistic or antagonistic effects and may also influence the response to a given level of toxin exposure. The effect of metabolites must also be considered. Many chemicals have metabolites that remain pharmacologically active. Some (e.g., acetaminophen, toxic alcohols, chlorinated hydrocarbons, meperidine, paraquat, and certain organophosphate insecticides) undergo metabolic activation, resulting in the production of compounds that are more toxic than the parent one.

Metabolism/Elimination

Elimination of chemicals from the body (detoxification) is accomplished by urinary, pulmonary, GI, and glandular (e.g., bile, milk, tears, saliva, sweat) excretion or metabolic inactivation. Hepatic metabolism and renal excretion are the major routes of elimination for most agents. Pulmonary excretion also plays a major role in the elimination of gases and volatile chemicals. Elimination generally follows first-order kinetics. For some toxins, hepatic metabolism has a finite capacity (i.e., becomes "saturated") and proceeds at a constant rate (zero-order kinetics). When the primary route of elimination is a zero-order metabolism, a small increase in dose can result in a large increase in blood and tissue concentrations and potential poisoning. Chemicals exhibiting such metabolism include alcohols, phenytoin, salicylate, and theophylline.

Renal excretion is accomplished by translocation processes (e.g., glomerular filtration, tubular secretion, and reabsorption) and is therefore influenced by the same factors as absorption and distribution. Any condition that impairs hepatic or renal blood flow or function can decrease toxin elimination. Metabolic enzymes are also subject to genetic influences and to induction or inhibition resulting from past or current chemical exposures. Regardless of the kinetics and route of elimination, the time required for elimination increases as the tissue concentration of chemical increases. *Hence, the duration of the effect tends to be longer after an overdose than after a therapeutic dose.*

CLINICAL CONSIDERATIONS

The principal objectives in the diagnosis and evaluation of the poisoning are recognition of an exposure or poisoning, identification of the offending agent(s), prediction of potential toxicity, and assessment of the severity of clinical effects. Treatment objectives include resuscitation, prevention of further absorption, enhancement of elimination, and the administration of antidotal therapy (Table 117.2).

TABLE 117.2

TREATMENT OBJECTIVES—GENERAL PRINCIPLES

1. Resuscitation
2. Prevention of further exposure
3. Enhanced elimination
4. Novel/antidotal therapy

Early accurate diagnosis is a prerequisite for optimal management.

The priority of assessment and treatment objectives depends on the phase of poisoning [28]. During the preclinical phase (i.e., the time between exposure and the onset of clinical or laboratory evidence of toxicity), management priorities include chemical identification, prediction of toxicity, and prevention of absorption (i.e., decontamination). The sooner decontamination is accomplished, the greater its efficacy. Hence, the physical examination and gathering of ancillary data should initially be brief. Assessment should focus on the exposure history, whether or not poisoning is likely to ensue, and whether or not decontamination is indicated.

During the toxic phase (i.e., the time between the onset of toxicity and its peak), assessment of the severity of poisoning, resuscitation, prevention of further absorption, enhancement of elimination, and antidotal therapy are the primary objectives. If the patient is critically ill, the history, physical examination, and diagnostic testing must be conducted concurrently with resuscitation.

During the resolution phase (i.e., the time between peak toxicity and full recovery), continued supportive care, enhancement of elimination, antidotal therapy, and reassessment of severity (i.e., evaluation of the response to treatment) are the most important management considerations. Measures to prevent subsequent reexposure should also be initiated before discharge.

Recognition of Poisoning

Although poisoning can cause a wide variety of nonspecific signs and symptoms, the diagnosis can usually be established by the history, physical examination, routine and toxicologic laboratory evaluation, and the clinical course. Ideally, criteria similar to Koch's postulates for infectious disease should be met: A chemical is identified in or on the body in an amount known to cause the observed signs and symptoms within the reported time frame. In reality, the diagnosis is often made on the basis of a history of exposure, a clinical course consistent with poisoning, and exclusion of other etiologies.

Making the diagnosis is easy when an accurate history of exposure is available. However, patients may be unaware of an exposure, unwilling to admit to one, or unable to give a history at all. Patients may give a history that is vague, confusing, or intentionally disguised.

Circumstances that should arouse suspicion of occult poisoning include sudden or unexplained illness in a previously healthy individual; similar unexplained symptoms in a group of individuals; a psychiatric history, alcoholism, or drug abuse; a recent change in health, economic status, or social relationships; and the onset of illness shortly after ingesting food, drink, or medication. Poisoning should always be considered in patients with metabolic abnormalities (especially acid–base disturbances), gastroenteritis, or changes in behavior or mental status of unclear etiology. Leakage of illicit drug packets that have been ingested or concealed in body cavities should be suspected in patients with altered mental status or unusual

behavior who have just arrived from abroad (especially Asia and South America) or who have recently been arrested or incarcerated for criminal activity [29,30]. Drug intoxication is a risk factor for trauma and suicide and should also be considered in all injured patients [31].

To avoid missing the diagnosis of poisoning, the physician must specifically inquire about toxin exposure. In suspicious cases, the physician should assume the role of detective to elicit historical support for the diagnosis [32]. Paramedics, police, and family, friends, employer, pharmacist, or personal physician can be questioned regarding the circumstances and events surrounding the illness, particularly the availability of chemicals and the likelihood of exposure. The patient's clothes and place of discovery should be searched for a suicide note, xenobiotics, and open or empty medication containers. Third parties should be instructed to search the house for such evidence and to bring it in for inspection.

In the absence of a history of exposure, the characteristic clinical course of poisoning may also suggest the diagnosis. Signs and symptoms of poisoning typically develop within minutes to an hour of an acute exposure, progress to a maximum within several hours, and gradually resolve over a period of hours to a few days. In such situations, toxicology screening (see later) may allow for a positive diagnosis if signs and symptoms are consistent with the known toxicity of the toxin(s) detected and other etiologies have been excluded.

Identification of the Offending Agent

History

The etiology of poisoning may or may not be disclosed by the patient history. Even when a history is available, its accuracy and reliability must be assessed. The identity of the toxin involved is incorrectly reported by up to 50% of patients with intentional ingestions [33]. The amount reportedly taken is also unreliable. Hence, in such patients, the history should be approached with caution. Layperson misidentification of acetaminophen as aspirin and vice versa is also relatively common. To avoid missing the correct diagnosis, the presence or absence of both drugs should be confirmed by laboratory analysis when an overdose of any kind is suspected.

Pill, Product, Plant, and Animal Identification

Drugs in pill form can often be identified by the imprint code, the alphabetical and numeric markings on tablets and capsules. A listing of imprint codes with the corresponding trade name and ingredient(s) can be found in the Identidex portion of *Poisindex* [27], which is available at virtually all poison centers in the United States. It also provides the identities of street drugs based on their slang names. Prescription drugs may be identified by contacting the dispensing pharmacy. Drug samples can sometimes be identified by direct chemical analysis (Toxicology Screening section). Police and government toxicology laboratories may be of assistance when illicit drug use is involved.

By US law [34], the ingredients of potentially hazardous commercial products used in and around the home must be stated on their label. This information, however, is not necessarily present or accurate, and labels may be missing or unreadable. In such cases, the ingredients may be identified by consulting *Poisindex* [27] or a regional poison center. Alternatively, the manufacturer or distributor can be called to obtain information on drugs or products that they produce or distribute. This action may be particularly helpful if the product is an outdated formulation or a recently reformulated or released one. Most large companies maintain 24-hour emergency telephone numbers for such purposes, and many employ medical consultants who can also provide management advice. Although industrial products do not have the same labeling requirements as household ones, right-to-know legislation requires that companies make information regarding the ingredients and potential toxicity of products they make, distribute, or use available to workers and health care providers [35]. Such information can be obtained by requesting a Material Data Safety Sheet (MSDS).

Information on drugs and chemical products manufactured or obtained outside the United States can be found in *Poisindex* [27] and *Martindale: The Complete Drug Reference* [21], or obtained from a domestic or foreign poison center. Information on drugs undergoing clinical trials in the United States may also be found in *Martindale*, since such drugs are often already available in other countries. Most foreign poison centers have English-speaking staff or translators available.

Plants (including fungi or mushrooms), along with their active parts and chemical constituents, can be identified by consulting *Poisindex* [27] if either their common or botanical name is known. If the name is not known but a sample is available, a representative from a local nursery, horticultural or mycologic society, or university botany department may be of assistance in identifying it. Similarly, pet stores, zoos, veterinarians, amateur or academic entomologists, herpetologists, zoologists, and field guides can be helpful in identifying potentially venomous insects, reptiles, snakes, and other animals. Poison centers usually maintain lists of local experts who are willing to help with such identifications.

Toxidromes

A toxidrome is a clinical syndrome that involves multiple physiologic systems and facilitates bedside identification of the culprit toxin [36]. The physiologic state of the patient can usually be characterized as excited (i.e., central nervous system [CNS] excitation with increased blood pressure, pulse, respirations, and temperature), depressed (i.e., decreased level of consciousness and decreased vital signs), discordant (i.e., inconsistent, mixed, or opposing CNS and vital sign abnormalities), or normal. The differential diagnosis can then be narrowed to the common or characteristic causes of these physiologic states (Table 117.3).

The *excited state* is primarily caused by sympathomimetics (agents that directly or indirectly stimulate α- and β-adrenergic receptors), anticholinergics (agents that block parasympathetic muscarinic receptors), hallucinogens, and withdrawal syndromes. The *depressed state* is primarily caused by sympatholytics (agents that block adrenergic receptors or depress cardiovascular activity), cholinergics (agents that directly or indirectly stimulate muscarinic receptors), opioids, or sedative hypnotics (which enhance the effect of the inhibitory CNS neurotransmitter gamma-aminobutyric acid [GABA] or depress neuronal membrane excitability). The *discordant state* is primarily due to asphyxiants (agents that decrease the availability, absorption, transport, or use of oxygen), membrane active agents (those that block sodium channels or otherwise alter the activity of excitable cell membranes), and agents that cause a variety of CNS syndromes due to interference with dopamine, GABA, glycine, or the synthesis, metabolism, or function of serotonin. A *normal physiologic state* may be due to a nontoxic exposure (Table 117.4), psychogenic illness, or presentation during the preclinical phase of poisoning. Agents that have a long preclinical phase (i.e., delayed onset of toxicity) are known as toxic "time bombs." Delayed onset of toxicity may result from slow absorption or distribution, metabolic activation, or a mechanism of action

TABLE 117.3

DIFFERENTIAL DIAGNOSIS OF POISONING BASED ON PHYSIOLOGIC ASSESSMENT AND UNDERLYING MECHANISMS

Excited (CNS stimulation with increased vital signs)	Depressed (CNS depression with decreased vital signs)	Discordant (mixed CNS and vital sign abnormalities)	Normal
Sympathomimetics Amphetamines Bronchodilators (β-agonists) Catecholamine analogues Cocaine Decongestants Ergot alkaloids Methylxanthines Monoamine oxidase inhibitors Thyroid hormones **Anticholinergics** Antihistamines Antispasmodics (GI-GU) Atropine and other belladonna alkaloids Cyclic antidepressants Cyclobenzaprine Mydriatics (topical) Nonprescription sleep aids Orphenadrine Parkinsonian therapeutics Phenothiazines Plants/mushrooms **Hallucinogens** LSD and tryptamine derivatives Marijuana Mescaline and amphetamine derivatives Psilocybin mushrooms Phencyclidine **Withdrawal syndromes** Baclofen β-Adrenergic blockers Clonidine Cyclic antidepressants Ethanol Opioids Sedative hypnotics	**Sympatholytics** α-Adrenergic antagonists Angiotensin-converting enzyme inhibitors β-Adrenergic blockers Calcium channel blockers Clonidine gestants Cyclic antidepressants Decongestants (imidazolines) Digitalis Neuroleptics **Cholinergics** Bethanechol Carbamate insecticides Echothiophate Myasthenia gravis therapeutics Nicotine Organophosphate insecticides Physostigmine Pilocarpine Urecholine **Opioids** Analgesics Antidiarrheal drugs Fentanyl and derivatives Heroin Opium **Sedative-hypnotics** Alcohols Anticonvulsants Barbiturates Benzodiazepines Bromide Ethchlorvynol GHB Glutethimide Methyprylon Muscle relaxants	**Asphyxiants** Carbon monoxide Cyanide Hydrogen sulfide Inert (simple) gases Irritant gases Methemoglobinemia Oxidative phosphorylation inhibitors Herbicides (nitrophenols) **AGMA inducers** Alcoholic ketoacidosis Ethylene glycol Iron Methanol (formaldehyde) Paraldehyde Metformin/phenformin (chronic) Salicylate Toluene Valproic acid **CNS syndromes** Disulfiram Extrapyramidal reactions Isoniazid (GABA lytic) Neuroleptic malignant syndrome Serotonin syndrome Solvents (hydrocarbons) Strychnine (glycinergic) **Membrane active agents** Amantadine Antiarrhythmics Beta-blockers Cyclic antidepressants Fluoride Heavy metals Lithium Local anesthetics Meperidine/propoxyphene Neuroleptics Quinine (antimalarials)	**Nontoxic exposure** **Psychogenic illness** **Toxic time bombs** Acetaminophen Agents that form concretions *Amanita phalloides* and related mushrooms Anticholinergics Cancer therapeutics Carbamazepine Chloramphenicol Chlorinated hydrocarbons Colchicine Digitalis preparations Dilantin kapseals Disulfiram Enteric-coated pills Ethylene glycol Heavy metals Fluoride Immunosuppressive agents Lithium Lomotil (atropine and diphenoxylate) Methanol Methemoglobin inducers (some) Monoamine oxidase inhibitors Paraquat Opioids Organophosphate insecticides (some) Podophyllin Salicylates Sustained-release formulations Thyroid hormone synthesis inhibitors Thyroxine valproic acid Viral antimicrobials

AGMA, anion gap metabolic acidosis; CNS, central nervous system; GABA, gamma-aminobutyric acid; GHB, gamma-hydroxybutyrate; GI–GU, gastrointestinal–genitourinary; LSD, lysergic acid diethylamide.

TABLE 117.4

CRITERIA FOR A NONTOXIC EXPOSURE

Patient is asymptomatic by both history and physical examination
Amount and identity of all chemicals and time of exposure are known with high degree of certainty
Exposure dose is less than the smallest dose known or predicted to cause toxicity

that involves the disruption of metabolic or synthetic pathways. Psychogenic illness should be considered when symptoms are inconsistent with the reported exposure and cannot be substantiated by objective physical findings, laboratory abnormalities, and toxicologic testing and other etiologies have been excluded [37].

An excited or depressed state may be mischaracterized as a discordant one when the activity of a stimulant or depressant is selective for a receptor subtype or results in a compensatory or opposing autonomic response. For example, hypotension caused by an alpha-blocker, β_2-agonist, or vasodilator may be

TABLE 117.5

PHYSIOLOGIC GRADING OF THE SEVERITY OF POISONING

	Signs and symptoms	
Severity	**Stimulant poisoning**	**Depressant poisoning**
Grade 1	Agitation, anxiety, diaphoresis, hyperreflexia, mydriasis, tremors	Ataxia, confusion, lethargy, weakness, verbal, able to follow commands
Grade 2	Confusion, fever, hyperactivity, hypertension, tachycardia, tachypnea	Mild coma (nonverbal but responsive to pain); brainstem and deep tendon reflexes intact
Grade 3	Delirium, hallucinations, hyperpyrexia, tachyarrhythmias	Moderate coma (respiratory depression, unresponsive to pain); some but not all reflexes absent
Grade 4	Coma, cardiovascular collapse, seizures	Deep coma (apnea, cardiovascular depression); all reflexes absent

accompanied by tachycardia, and hypertension due to a selective α-agonist (e.g., phenylpropanolamine) may be accompanied by bradycardia. Severe stimulant or depressant poisoning can also cause what appears to be a discordant state (Table 117.5). For example, prolonged seizures and extreme hyperthermia caused by sympathomimetics can culminate in cardiovascular collapse as a consequence of anaerobic metabolism, acidosis, or depletion of neurotransmitters. Similarly, marked hypotension and hypoventilation caused by physiologic depressants can precipitate seizures and tachyarrhythmias as a result of ischemia, anoxia, and acidosis. In addition, paradoxic excitation can result from the preferential inhibition of cortical function that normally controls social activity by low doses of CNS depressants, most notably alcohol and other sedative hypnotics. In such cases, the physiologic state and its cause can often be correctly identified by the overall clinical picture and course of events.

The severity of mental status changes and the nature of associated autonomic findings can be used to narrow the differential diagnosis of physiological stimulation and depression to one of four subcategories (see Table 117.3). In the excited patient, marked vital sign abnormalities (e.g., severe hypertension with end-organ ischemia, tachyarrhythmias, hyperthermia, cardiovascular collapse) with minor mental status changes suggest an agent with peripheral sympathomimetic activity as the cause. Conversely, marked mental status abnormalities with nearly normal vital signs suggest a centrally acting hallucinogen. Anticholinergic poisoning (Table 117.6) can be differentiated from sympathomimetic (Table 117.7), hallucinogen, and withdrawal syndromes by the presence of dry, flushed, and hot skin; decreased or absent bowel sounds; and urinary retention. Other causes of excitation are usually accompanied by pallor, diaphoresis, and increased bowel or bladder activity.

In the patient with physiological depression, marked cardiovascular abnormalities (e.g., hypotension and bradycardia) with relatively clear sensorium suggest a peripherally acting sympatholytic, whereas marked CNS and respiratory depression with minimal pulse and blood pressure abnormalities suggest a centrally acting agent (opioid or sedative hypnotic). Cholinergic poisoning (Table 117.8) can be distinguished from other causes of physiologic depression by the presence of characteristic autonomic findings: *S*alivation, *l*acrimation, *u*rination, *d*efecation, *G*I cramps, and *e*mesis (SLUDGE syndrome). In addition, cholinergic poisoning causes pallor and diaphoresis, whereas the skin is usually warm and dry with opioid and sedative–hypnotic poisoning.

Other findings can sometimes help narrow the differential diagnosis further. Only the most common and diagnostically useful ones are noted here. Because of limited specificity and sensitivity, the presence or absence of a particular sign or symptom cannot be used to confirm or exclude a given etiology.

Ocular findings can sometimes help narrow the diagnostic possibilities. Although mydriasis can be caused by any agent or condition that results in physiologic excitation (see Table 117.3), it is most pronounced in anticholinergic poisoning, in which it is associated with minimal pupil response to light and accommodation. Similarly, although miosis is a nonspecific manifestation of physiologic depression, it is usually most pronounced in opioid poisoning. Notable miosis can, however, also be caused by cholinergic agents and sympatholytics with alpha-blocking effects (e.g., phenothiazines). Visual disturbances suggest anticholinergic, cholinergic, digitalis, hallucinogen, methanol, and quinine poisoning. Horizontal nystagmus and disconjugate gaze are nonspecific manifestations

TABLE 117.6

ANTICHOLINERGIC TOXIDROME

Tachycardia
Hyperthermia
Hallucination/confusion
Dry mouth/garbled speech
Mydriasis
Ileus
Urinary retention
Dry, flushed skin

TABLE 117.7

SYMPATHOMIMETIC TOXIDROME

Mydriasis
Agitation
Diaphoresis
Hypertension
Hyperthermia
Tachycardia

TABLE 117.8

CHOLINERGIC TOXIDROME

Salivation
Lacrimation
Urination
Defecation
GI cramps
Emesis

of sedative–hypnotic poisoning. Although vertical and rotary nystagmus can be seen in patients with lithium and phenytoin poisoning, they are most suggestive of phencyclidine intoxication. These etiologies should be readily distinguishable by assessing the physiologic state. Rapidly alternating lateral "ping-pong" gaze has been described in monoamine oxidase inhibitor poisoning. Except for abnormalities due to topical chemical exposure, both eyes are equally affected. Although failure to respond to topical miotics has been said to be diagnostic of drug-induced pupillary dilatation, this is only true for topical exposures. Hence, unilateral pupillary abnormalities should generally prompt evaluation for a central, structural lesion.

Dermatologic abnormalities may also be helpful. Flushed skin can be caused by anticholinergics, boric acid, a disulfiram-ethanol reaction, monosodium glutamate, niacin, scombroid (fish poisoning), and rapid infusion of vancomycin (red man syndrome). The skin is hot and dry in anticholinergic poisoning but normal or moist with other etiologies. Flushing should not be confused with the orange skin discoloration caused by rifampin. Pallor and diaphoresis may be due to cholinergics, hallucinogens, hypoglycemics, sympathomimetics, and drug withdrawal (see Table 117.3). As noted previously, manifestations of the SLUDGE syndrome distinguish cholinergic poisoning from other etiologies. Cyanosis may be due to agents that cause cardiovascular or respiratory depression, methemoglobinemia, pneumonitis, or simple asphyxia. In methemoglobinemia, it may have a chocolate-brown or slate-gray hue and is unaffected by oxygen administration. Cyanosis should not be confused with the blue discoloration of the skin caused by amiodarone or by topical exposure to blue dyes. The latter condition can be diagnosed by wiping the skin with acetone or alcohol. Hair loss, mucosal pigmentation, and nail abnormalities are suggestive of heavy metal poisoning (e.g., arsenic, lead, mercury, thallium).

Finally, the presence of neuromuscular abnormalities may suggest certain etiologies. Seizures and tremors can be caused by cholinergics, hypoglycemic agents, lithium, membrane-active agents, some narcotics (e.g., meperidine, propoxyphene), and most physiologic stimulants [38] (see Table 117.3). They can also occur in patients poisoned by agents that cause asphyxia, low lactate increased AGMA (see later), and cerebral hypoperfusion or hypoventilation (e.g., physiologic depressants; see Table 117.3). The most common causes of seizures due to poisoning are tricyclic antidepressants, sympathomimetics, antihistamines (primarily diphenhydramine), theophylline, and isoniazid. Although carbon monoxide, hypoglycemics, lithium, and theophylline can cause focal seizures, seizures due to poisoning are usually generalized. Because hypertensive and traumatic CNS hemorrhages are known complications of poisoning, the possibility of a structural lesion should be considered if focal signs and symptoms are present. Myoclonus suggests anticholinergic or sympathomimetic poisoning. Fasciculations are typical of cholinergic insecticide poisoning but can also be caused by sympathomimetics. Rigidity may be seen in phencyclidine and sympathomimetic poisoning and in those with CNS syndromes (see Table 117.3). Dystonic posturing is most often caused by antipsychotic agents. It is also a characteristic feature of strychnine poisoning.

Laboratory Findings

Acid–base status, anion gap, serum osmolality, ketone, electrolyte, glucose, and organ function abnormalities identified by routine laboratory tests can be extremely helpful in the differential diagnosis of poisoning. As with clinical manifestations, the diagnostic sensitivity and specificity of a single finding is not sufficiently high for its presence or absence to confirm or exclude a specific etiology. The use of anion and osmolar gaps and serum ketone and lactate levels in the diagnosis of poisoning of unknown etiology is summarized in Figure 117.1.

Assessing acid–base status and calculating the anion gap is particularly important because an increased AGMA may be due to advanced ethylene glycol, methanol, and salicylate poisoning. In such cases, prompt initiation of specific therapies is essential to prevent progressive, irreversible, or fatal poisoning [39,40]. The normal anion gap is 13 ± 4 mEq per L in unselected acutely hospitalized patients. In ethylene glycol and methanol poisoning, AGMA is primarily due to the accumulation of acid metabolites. In salicylate poisoning, it is caused by the accumulation of a variety of endogenous organic acids resulting from salicylate's interference with intermediary metabolism. Agents that cause hypoxemia, cellular asphyxia, seizures, shock, or extensive tissue necrosis can also cause an AGMA, but in these instances, the accumulation of lactic acid generated by anaerobic metabolism is responsible for the AGMA. When the underlying cause is unclear, measuring the serum lactate level may be helpful. The lactate concentration is usually low (< 5 mEq per L) or significantly less than the anion gap in ethylene glycol, methanol, and salicylate poisoning, but high (> 5 mEq per L) or nearly equal to the anion gap in conditions associated with anaerobic metabolism.

Other common toxicologic causes of a low-lactate AGMA include ethanol, which can cause ketoacidosis by disrupting intermediary metabolism in susceptible alcoholics, and toluene, which can cause renal tubular acidosis with bicarbonate wasting. Rarely, this metabolic picture occurs in poisoning by formaldehyde (which is metabolized to formic acid), paraldehyde (presumably as a result of its metabolism to acetic acid), phosphate [41], and sulfur (and possibly sulfates) [42]. It can also be seen with large overdoses of ibuprofen (and probably all nonsteroidal anti-inflammatory agents) and valproic acid (due to high levels of these acidic drugs and their metabolites) [43,44]. Metformin and nucleoside reverse transcriptase inhibitor antiretroviral agents (e.g., zidovudine or azidothymidine) can interfere with normal-lactate metabolism and cause a high-lactate AGMA at therapeutic as well as excessive doses [45,46]. A high-lactate AGMA can rarely occur soon after massive acetaminophen ingestion [47].

An abnormally low anion gap may be seen in severe bromide, calcium, iodine, lithium, magnesium, and nitrate intoxication [39,48,49]. In bromide, iodine, and lithium intoxication, the low anion gap results from spuriously elevated chloride levels, and with nitrate poisoning, it is due to falsely elevated bicarbonate levels.

Serum osmolality can help differentiate the toxic causes of a low-lactate AGMA. An increased osmole gap may be seen early in the course of ethylene glycol and methanol (when high serum levels of the parent compounds are present) but not salicylate poisoning. Although not strictly accurate from a physical chemistry perspective [50], the osmole gap is typically defined

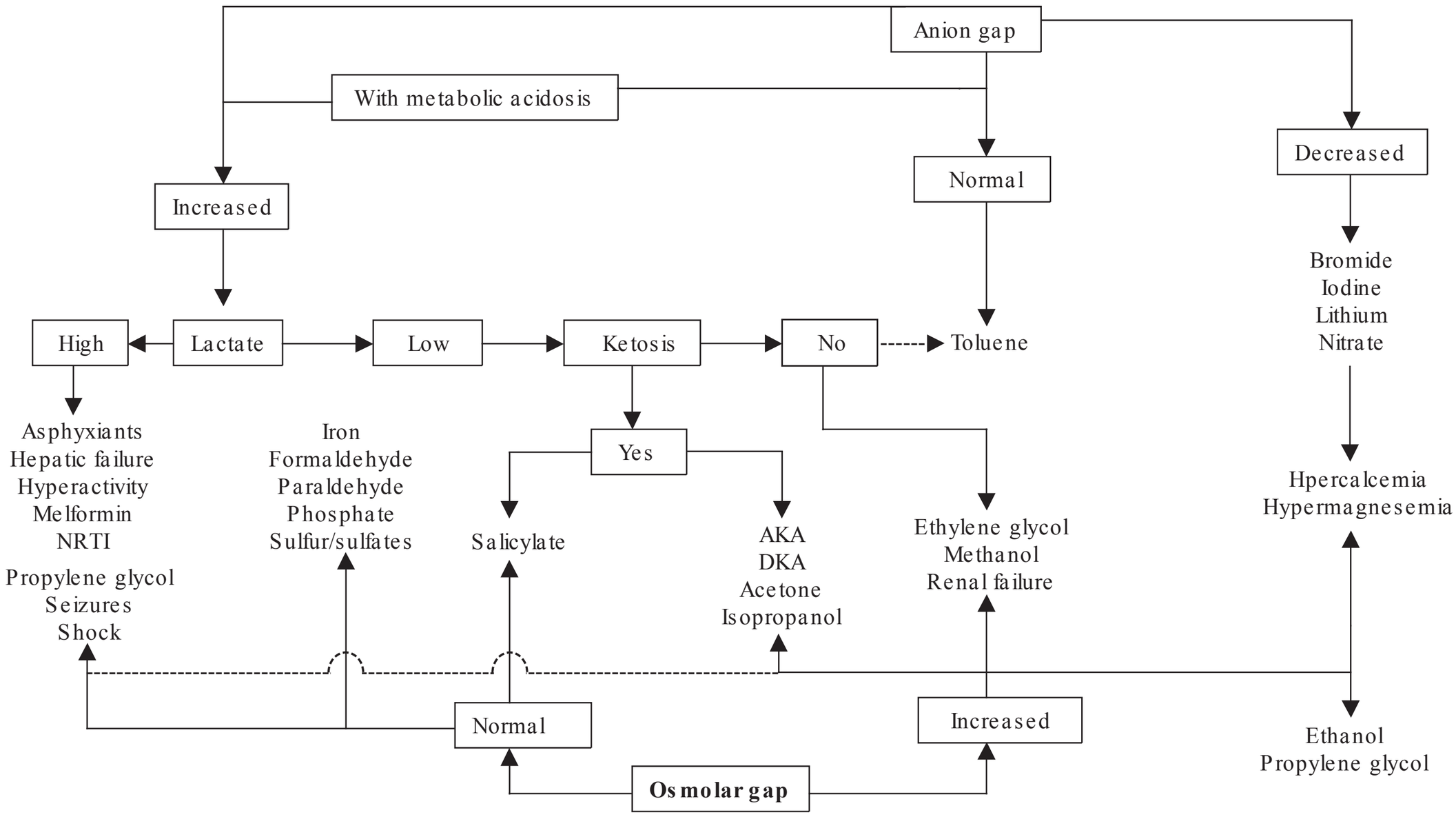

FIGURE 117.1. Use of routine laboratory findings and calculated gaps in the differential diagnosis of poisonings. AKA, alcoholic ketoacidosis; DKA, diabetic ketoacidosis; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors.

as the difference between the measured serum osmolality and the calculated serum osmolality.

$$\text{Serum Osmolality } (\mu\text{mol/L}) = 2\,(\text{serum Na}) + \text{serum glucose} + \text{serum BUN}$$

where normal serum osmolality is 290 ± 10 mOsm per kg of H_2O normal osmole gap is 5 ± 7 mOsm per kg (in unselected acutely hospitalized patients [40]).

$$\text{Osmole gap} = [\text{calculated serum osmolality} - \text{measured serum osmolality}]$$

Normal osmole gap is 5 ± 7 mOsm per kg (in unselected hospitalized patients [40])

This formula assumes that all concentrations are measured in millimoles per liter. If the glucose and BUN concentrations are measured in milligrams per deciliter, dividing them by 18 and 3, respectively, gives their approximate concentrations in millimoles.

Additional causes of an increased osmolar gap include other low-molecular-weight solutes, such as acetone, ethanol, isopropyl alcohol, magnesium, mannitol, and propylene glycol [51]. The approximate concentration of these substances that will increase the serum osmolality by 1 mOsm per kg of H_2O, calculated on the basis of their molecular weights, is shown in Table 117.9. When direct measurements are not readily available, the serum concentration of these agents can be estimated by multiplying this amount by the osmolar gap. Serum osmolality must be measured by freezing point depression rather than the headspace or vapor pressure method to detect the presence of volatile agents such as acetone and toxic alcohols. An increased osmolar gap has also been reported in alcoholic ketoacidosis and conditions causing lactic acidosis [52].

Serum ketones can also help to differentiate the toxic causes of a low-lactate AGMA. Ketosis, as defined by a positive nitroprusside reaction, is relatively common in salicylate poisoning but unusual in ethylene glycol and methanol poisoning. Ketosis is also seen in alcoholic ketoacidosis and in acetone and isopropyl alcohol poisoning.

The urinalysis, serum calcium concentration, and the overall clinical picture can also be helpful in differentiating the toxic causes of a low-lactate AGMA. Crystalluria, hypocalcemia, and back pain or flank tenderness suggest ethylene glycol; visual symptoms implicate methanol; and tinnitus or impaired

TABLE 117.9

EFFECTS OF SOME SOLUTES ON SERUM OSMOLALITY

Solute	Approximate concentration required to increase serum osmolality by 1 mOsm/kg
Alcohols, glycols, and ketones	
Acetone	5.8 mg/dL
Ethanol	4.6 mg/dL
Ethylene glycol	5.2 mg/dL
Isopropanol	6.0 mg/dL
Methanol	2.6 mg/dL
Propylene glycol	7.6 mg/dL
Electrolytes	
Calcium	4.0 mg/dL (1 mEq/L)
Magnesium	2.4 mg/dL (1 mEq/L)
Sugars	
Mannitol	18 mg/dL
Sorbitol	18 mg/dL

hearing point to salicylates. Crystalluria can also be caused by acyclovir [53], felbamate [54], indinavir [55], oxalate [56], primidone [57], and sulfa drugs [58]. Hypocalcemia is also seen in fluoride and oxalate [56] intoxication.

Serum potassium and glucose abnormalities may also provide clues to the etiology of poisoning [18,59,60]. Toxicologic causes of hypokalemia include barium, β_2-adrenergic agonists, calcium channel blockers, chloroquine, diuretics, insulin, licorice, methylxanthines, and toluene. Hyperkalemia can be caused by α-adrenergic agonists, angiotensin-converting enzyme inhibitors, beta-blockers, digitalis, fluoride, potassium-sparing diuretics, and trimethoprim. Common toxicologic causes of hypoglycemia are ethanol, beta-blockers, hypoglycemics, quinine, and salicylate. Common causes of hyperglycemia include acetone, β-agonists, calcium channel blockers, iron, and methylxanthines.

Common toxicologic causes of acute liver dysfunction are acetaminophen, ethanol, halogenated hydrocarbons (e.g., carbon tetrachloride), heavy metals, and mushrooms (e.g., *Amanita phalloides* and related species) [61]. Acute renal toxicity is most often due to ethylene glycol, halogenated hydrocarbons, heavy metals, nonsteroidal anti-inflammatory drugs, toluene, envenomations, and agents that cause hemolysis or rhabdomyolysis [62]. An elevated creatinine with a normal BUN can be seen in acetone and isopropyl alcohol poisoning because acetone interferes with colorimetric assays for creatinine, resulting in falsely high results. Acute hemolysis (in the absence of glucose-6-phosphate dehydrogenase deficiency) can result from poisoning by arsine gas, naphthalene, and inducers of methemoglobinemia. Rhabdomyolysis is associated with toluene abuse, CNS syndromes (see Table 117.3), and severe physiologic dysfunction (e.g., extreme agitation, deep or prolonged coma, hyperthermia, seizures) of any etiology [63]. The most common agents involved are sympathomimetics, ethanol, heroin, and phencyclidine.

Electrocardiographic Findings

The ECG may provide clues to the cause of poisoning [18]. Ventricular tachyarrhythmias that occur in patients with normal QRS and QT intervals suggest myocardial irritation (i.e., increased automaticity) as the underlying mechanism. Sympathomimetics, digitalis, and cardiac-sensitizing agents such as chloral hydrate and aliphatic or halogenated hydrocarbons, which potentiate the action of endogenous catecholamines, are common causes [64]. In contrast, ventricular tachyarrhythmias that occur in the setting of depolarization and repolarization abnormalities, reflected by QRS and QT interval prolongation, respectively, suggest a reentrant mechanism. Causes include electrolyte abnormalities, organophosphate insecticides, and other membrane active agents (see Table 117.1) [65,66]. Torsades de pointes (polymorphous) ventricular tachycardia strongly implicates an agent that prolongs the QT interval.

Atrioventricular conduction abnormalities (atrioventricular block) and bradyarrhythmias can be caused by beta-blockers, calcium channel blockers, digitalis, membrane-active psychotherapeutic agents, organophosphate insecticides, and α-agonists such as phenylpropanolamine. With α-agonists, they are a reflex (i.e., homeostatic) response to hypertension, but with other causes, they are associated with generalized cardiovascular depression and hypotension.

Radiologic Findings

Ingested chemicals can sometimes be visualized within the GI tract by abdominal radiographic imaging, and such imaging can occasionally be helpful in suggesting the etiology or amount of an unknown ingestion. Although a large variety of chemicals can be detected by routine radiography in vitro, relatively few are visible in vivo [67]. Agents most likely to be visible on plain films are indicated by the mnemonic CHIPES (Table 117.10) [18].

TABLE 117.10

XENOBIOTICS VISIBLE ON PLAIN STOMACH RADIOGRAPHS

Chlorinated hydrocarbons
Heavy metals
Iodinated compounds
Packets of drugs
Enteric-coated drugs
Salicylates

Ingested drug packets may appear as uniform, ovoid or round, marble-sized densities scattered along the GI tract [29,30]. Ingested hydrocarbons may sometimes appear as a double gastric fluid level or "double bubble" because of the air–fluid and fluid–fluid interface lines created when less dense hydrocarbons layer on top of gastric fluids. Computed tomography may be superior to plain films in detecting ingested drug packets but the optimal test in this setting remains unclear [68,69]. Whether contrast should be used or not remains controversial. Abdominal ultrasound can detect ingested pills, particularly enteric-coated and sustained-released formulations [70]. Such imaging may be useful in confirming or refuting some recent specific (CHIPES) ingestions. Because the volume of pills can be determined, plain radiography may be used to guide GI decontamination.

Abnormal findings on chest radiography can be caused by a wide variety of chemicals [18,71]. Diffuse or patchy infiltrates (i.e., pneumonitis or acute lung injury) can be due to the inhalation of irritant gases (e.g., ammonia, chlorine, hydrogen sulfide, nitrogen oxides, phosgene, smoke, sulfur dioxide), fumes (e.g., beryllium, metal oxides, polymers), and vapors (e.g., acids, aldehydes, hydrocarbons, isocyanates, mercury). They can also be seen in patients who have ingested or injected cholinergic agents (e.g., carbamate and organophosphate insecticides), metabolic poisons (e.g., cyanide, carbon monoxide, heavy metals, hydrogen sulfide), paraquat, phencyclidine, salicylates, thiazide diuretics, and tocolytics and in patients with envenomations. Aspiration pneumonitis is quite common and can occur in patients with coma or seizures of any etiology [72]. Acute lung injury can also develop in any patient with prolonged or pronounced anoxia, hyperthermia, or hypotension (e.g., those with severe opioids or sedative–hypnotic or sympathomimetic poisoning). Chronic chemical exposure can cause pulmonary fibrosis, granulomas, or pleural plaques.

Response to Antidotes

The use of antidotes for diagnostic purposes has largely fallen from favor. The availability of point of care blood glucose measurement negates the need for empiric intravenous dextrose in altered patients. Many antidotes may be harmful if used inappropriately, including flumazenil physostigmine, glucagon, nitrites, and chelators. Naloxone remains a reasonably safe therapy in a patient with clinical signs of opiate intoxication. Clinicians should be prepared to manage acute withdrawal and its sequelae.

Toxicology Screening

Analysis of a sample of the toxin itself, or patient urine, blood, gastric contents, or hair [71,73] can sometimes be helpful in identifying the cause of poisoning. Urine is generally the best specimen to analyze because large quantities can be obtained

for extraction procedures and many chemicals are normally concentrated in urine. However, toxicology testing can detect only a small fraction of all chemicals (primarily drugs) and is not always reliable [74]. Immunoassay screens are inexpensive and provide results within minutes, but they are only capable of detecting a few agents. They suffer from many false positives and false negatives. Patients may be misdiagnosed and potentially harmed by clinicians acting solely on the results of immunoassay screens [75]. Comprehensive screens are expensive and require 2 to 6 hours for completion (excluding transportation times). Although results may increase diagnostic certainty or specificity, they rarely change disposition or treatment in patients who are asymptomatic or who have signs and symptoms consistent with the reported exposure [75–80]. Noteworthy exceptions are acetaminophen and salicylate, which are widely available, commonly ingested, sometimes misidentified, require specific treatment, and cause few or nonspecific early signs and symptoms. Hence, in most overdose patients, quantitative acetaminophen and salicylate levels are the only toxicology tests likely to be clinically useful.

Critically ill poisoned patients suffering seizures, cardiovascular instability, acid–base abnormalities, multiple organ dysfunction, nonsinus cardiac rhythms, or cardiac conduction disturbance without a toxicologic diagnosis should generally have comprehensive toxicology screening.

Knowledge of the methods used for chemical detection (e.g., colorimetric spot tests; thin-layer paper or plate chromatography; gas- or high-pressure liquid chromatography; absorbance, atomic absorption, flame ionization, or fluorometric assays; enzyme-multiplied and radionuclide immunoassays; gas chromatography with mass spectrometry) is required for accurate interpretation of the results of screening tests [75,81–83]. A positive result on one assay should always be confirmed by repeat analysis using a different technique. The physician should speak directly with the laboratory technician to determine which chemicals can be detected by the screening methods used and the sensitivity and specificity of each assay. In addition, directed analysis (e.g., coma, hallucinogen, or stimulant screen), with more rapidly available results, can be performed if the technician and clinician communicate.

A negative result from a screen should never be used to exclude the diagnosis of poisoning when clinical findings suggest otherwise. It may simply mean a chemical is not detectable by the assay(s) used, its concentration is below the limit of detection of the assay(s), or its concentration is too low to be confirmed. It may also mean the time of sampling or the specimen submitted is inappropriate for testing (e.g., the chemical may be undergoing absorption and is not yet present in urine or it may already have been metabolized or eliminated). In such cases, repeating the test on a sample obtained at an earlier or later time may be revealing.

Prediction of Potential Toxicity

The prediction of toxicity requires knowledge of the dose, time, and identity of an exposure and is necessary for determining the appropriate treatment. For commercial products, the amount and concentration of every ingredient should be identified. Household products deemed hazardous by the US Consumer Product Safety Committee are required by law to bear a label describing the nature of their toxicity and first aid measures as well as a "keep out of reach of children" warning and a signal word that indicates the degree or severity of potential toxicity [34]. The signal words "caution," "warning," and "danger" identify a product or its constituent(s) as a weak irritant (i.e., may damage mucosal surfaces), strong irritant (i.e., can damage skin and mucosa), or corrosive (i.e., can cause permanent tissue damage or death) after topical exposure or moderately toxic, highly toxic, or extremely toxic (oral median lethal dose: 50 to 500 mg per kg, 1 to 50 mg per kg, or < 1 mg per kg, respectively) after ingestion. Label information is frequently inaccurate or incomplete [34,84] and should generally be confirmed by consulting an independent information source.

The dose of drug in a pill or tablet can be determined using the resources cited in "Identification of the Offending Agent" section of this chapter. For liquids and powders, the dose can be estimated or measured using the container or the weights and volumes listed on the label. An exposure may also be reported in tablespoons or swallows. Standard flatware volumes can vary from 3 to 7 mL for a teaspoon and from 7 to 14 mL for a tablespoon. The volume of a swallow varies with age, height, weight, sex, the orifice size of the container, and the viscosity of the ingested liquid and ranges from 1 to 5 mL in infants to 4 to 40 mL in adults [85].

The accuracy and reliability of the history must be evaluated when assessing potential toxicity. The amount and time of ingestion are frequently erroneous when reported by patients with intentional self-poisoning. It is best always to assume a worst-case scenario: that the maximum possible dose (i.e., the entire amount available or not clearly accounted for) was ingested. The potential toxicity can then be estimated from previously reported toxicodynamic data. For drugs with CNS and cardiovascular activity, the ingestion of 5 to 10 therapeutic doses by an adult and one adult dose by a young child can result in significant toxicity. Beta-blockers, calcium channel blockers, and oral hypoglycemics can cause toxicity after only one or two therapeutic doses, particularly in those physiologically naïve to their effects. The ingestion of only one to two tablets, capsules, or teaspoonfuls of an antimalarial (e.g., chloroquine, hydroxychloroquine), antipsychotic (e.g., chlorpromazine, thioridazine), camphor, calcium channel blocker, methyl salicylate, opioid, oral hypoglycemic, theophylline, or tricyclic antidepressant (e.g., imipramine, desipramine) can be fatal to a toddler [86].

The time of exposure is important because it allows for prediction of the time of onset of toxicity and the time of peak toxicity. Only when the time elapsed since exposure clearly exceeds the longest reported or predicted interval between exposure and peak toxicity should the possibility of subsequent poisoning be excluded (see Table 117.5). Peak toxicity usually occurs within 4 to 6 hours of an oral overdose. Important exceptions to this generalization are the toxic time bombs described earlier. For some of these agents (e.g., acetaminophen, ethylene glycol, methanol, paraquat), the serum concentration measured during the preclinical phase can be used to predict subsequent toxicity. Peak toxicity may also be delayed (up to 12 to 24 hours) after exposure to irritants and corrosives. The possibility of pregnancy and potential toxicity to the fetus should also be considered.

Assessment of Severity

The severity of poisoning is primarily determined by findings on physical examination. Because poisoning is far more dynamic than most diseases and illnesses, frequent reevaluations are required. Poisoned patients can rapidly deteriorate, with few or no warning signs.

A complete physical examination should ultimately be performed in all patients. The examination should initially be directed toward assessment of cardiovascular stability, respiratory function, and neurologic status. Accurate and timely measurement of all vital signs is essential. The respiratory rate should be measured for a full minute. A core or rectal temperature should be obtained to detect severe or occult abnormalities. The sickest patients are the ones most likely to have significant temperature abnormalities. They are also the ones in

whom preoccupation with cardiovascular and respiratory therapy can lead to delayed temperature measurement. In contrast, an abbreviated mental status examination is usually sufficient. The degree of physiologic dysfunction should be objectively described.

The number and type of ancillary tests required to assess metabolic or organ function is determined primarily by clinical severity and secondarily by the history. Asymptomatic but potentially poisoned patients with reliable histories and unintentional exposures should have blood and urine samples obtained on presentation. Samples can be saved and subsequently sent for (baseline) analysis in the event of deterioration. Pregnancy testing, however, is recommended in all susceptible women of childbearing age. Patients who are symptomatic or suicidal should have serum electrolytes, BUN, creatinine, and glucose measurements; urinalysis; and 12-lead ECG. Arterial blood gas, serum osmolality, and ketone and methemoglobin analyses may also be indicated. Anion, osmolal, and oxygen saturation gaps should be calculated whenever their determinants are measured. Assessment of patients with respiratory complaints or grade 2 or greater stimulant or depressant poisoning (see Table 117.5) should include a chest radiograph. A complete blood cell count, coagulation studies, serum amylase, calcium, magnesium, creatine phosphokinase, and hepatic enzyme levels should also be determined in any patient with grade 2 or greater physiologic dysfunction. Additional testing (e.g., biopsies, invasive monitoring, neurodiagnostic studies, radiologic examinations) should be individualized and based on the findings of physical examination, the history, and the results of routine ancillary studies.

The measurement of chemical concentrations in serum, whole blood, or urine can sometimes help in assessing the severity of poisoning. Agents for which quantitative measurements are necessary or desirable for optimal patient management include acetaminophen, acetone, alcohols, antiarrhythmics, antiepileptics, barbiturates, carbon monoxide, digoxin, electrolytes (including calcium and magnesium), ethylene glycol, heavy metals, lithium, salicylate, and theophylline [75,81]. Quantitative or qualitative assays for other toxins are not generally helpful because they serve only to confirm the clinical impression and do not affect treatment (which is either supportive or must be initiated long before laboratory results are available in order to be effective).

Provision of Supportive Care

Meticulous supportive care is necessary to maintain physiologic and biochemical homeostasis and to prevent secondary complications (e.g., anoxia, aspiration, bedsores, shock-induced organ injury, sepsis) until detoxification can be accomplished by normal mechanisms or therapeutic interventions. Despite advances in preventing absorption, enhancing elimination, and antidotal treatment, supportive care remains the most effective therapy for most poisoned patients. Details of supportive therapy (e.g., treatment of vital sign abnormalities and organ dysfunction) can be found in other chapters. Only considerations of special relevance to the poisoned patient are discussed here.

Monitoring

Unless toxicity is minimal and predicted with a high degree of certainty to remain so, venous access should be established and continuous cardiac monitoring initiated. Because fluid resuscitation may become necessary, normal saline is the preferred IV solution. Pulse oximetry should be performed on presentation and monitored frequently if abnormal or significant (grade 2 or greater) physiologic dysfunction (see Table 117.5) is present. Until the ultimate severity of poisoning is known, frequent or continuous visual observation is also necessary. Patients with intentional self-poisoning also need close behavioral observation until the possibility of a repeat suicide attempt has been evaluated in detail and assessed to be unlikely.

Respiratory Care

Pulmonary aspiration of gastric contents is a relatively common complication of poisoning and its treatment (e.g., GI decontamination procedures) [87,88]. Patients with CNS depression or seizures are at risk for aspiration and airway obstruction. Although spontaneously breathing patients who respond to painful stimulation can sometimes be successfully managed by aspiration-preventative positioning (e.g., left lateral decubitus and Trendelenburg position) and close observation, definitive airway management is recommended for those who cannot respond by voice. Using the gag reflex to assess the need for intubation should be abandoned [87]. Many normal individuals have an absent gag reflex, and many comatose patients will gag if sufficiently stimulated and yet be unable to protect their airway. In addition, attempting to elicit a gag reflex may itself induce vomiting and cause aspiration in a patient with an altered mental state. Prophylactic or therapeutic intubation may also be required for patients with extreme behavioral or physiologic stimulation who require aggressive pharmacologic therapy with sedative, antipsychotic, anticonvulsant, or paralyzing agents. Even in comatose patients, pretreatment with a sedative and neuromuscular blocking agent can facilitate intubation [88]. An endotracheal tube with a low-pressure high-volume cuff is recommended to reduce aspiration, but it is by no means completely effective [89]. In intubated patients who can tolerate it, elevating the head of the bed may decrease the incidence of aspiration [90]. Extracorporeal membrane oxygenation, cardiopulmonary bypass, nitric oxide, prone positioning, and oscillation should be considered in patients with reversible poisoning who cannot otherwise be adequately oxygenated or ventilated.

Cardiovascular Therapy

Because of adverse drug interactions, therapy intended to maintain or restore normal blood pressure, pulse, and sinus rhythm may worsen, rather than alleviate, cardiovascular toxicity. Hence, the severity and trend of cardiovascular abnormalities and the potential complications of treatment should be considered before instituting pharmacologic therapy. In addition, because the causes of cardiovascular toxicity are varied and multiple mechanisms may be concurrently operative, invasive hemodynamic monitoring may be necessary for accurate diagnosis and optimal treatment. Aggressive supportive measures, such as transvenous cardiac pacing and intra-aortic balloon pump or cardiopulmonary bypass should be considered in patients with reversible poisoning who are unresponsive to routine therapeutic measures [91].

In the absence of extremes of heart rate, hypotension due to poisoning is most often caused by loss of peripheral vascular tone rather than pump failure. Bedside echocardiography can also be useful to assess cardiac output. Norepinephrine is generally considered the first line vasopressor in patients who do not respond to fluid administration.

When hypertension causes end organ dysfunction, therapy is indicated. In patients with sympathomimetic poisoning, beta-blockade may result in unopposed α receptor stimulation. This leads to increased peripheral vascular resistance, increasing the demand on a beta blocked heart. Hence, treatment with a non-selective sympatholytic or with an arteriodilator followed by a beta blocker is preferred.

Sinus tachycardia can usually be managed with sympatholytics. In patients with sympathomimetic poisoning and

signs or symptoms of myocardial ischemia, a beta-blocker (with or without an arteriodilator, depending on the presence or absence of coexisting hypertension) or a calcium channel blocker can be used.

Lidocaine is generally first line therapy for ventricular tachyarrhythmias. Underlying electrolyte and metabolic abnormalities should be corrected. Sodium bicarbonate or hypertonic saline may be effective in treating wide-complex tachycardias due to toxins with sodium channel blocking properties.

Normalizing electrolytes and continuous electrocardiographic monitoring is the mainstay of treatment for toxins that prolong the QT interval. The clinician must be prepared to manage Torsades des Pointes. Antibodies are available to treat serious dysrhythmias caused by cardiac glycosides. Magnesium may also be effective in digitalis poisoning. Procainamide, other class 1 A agents, beta-blockers, and physostigmine should not be used for arrhythmias caused by membrane-active agents or those associated with prolonged QRS or QT intervals because of the potential for worsening rhythm disturbances and conduction abnormalities.

Bradycardia requires treatment only if it is associated with hemodynamic instability. In most cases, atropine, dopamine, and epinephrine are the agents of choice. Calcium, glucagon, and high dose insulin can be effective in calcium channel blocker and beta-blocker poisoning.

Treatment of Neuromuscular Hyperactivity

Profound metabolic acidosis and sudden cardiac arrest can occur in patients with severe agitation who continue to struggle while being physically restrained. Prompt pharmacologic treatment of behavioral and muscular hyperactivity in such patients is critical. In general, benzodiazepines are preferred to antipsychotic agents because the latter lower the seizure threshold and prolong QTc. In phencyclidine poisoning, however, haloperidol, a central dopaminergic antagonist, may be more effective than benzodiazepines because phencyclidine has central dopaminergic activity. Similarly, chlorpromazine may be more effective than benzodiazepines in hallucinogen poisoning. The combined use of benzodiazepines and neuroleptics can be more effective than either alone; doses and side effects can often be minimized using this approach. For agitation and hallucinations due to anticholinergic poisoning, physostigmine may be considered.

Seizures can usually be effectively treated with GABA agonists such as benzodiazepines and barbiturates. Pyridoxine is usually necessary in isoniazid poisoning. Phenytoin, a Vaughn–Williams class 2 anticonvulsant, should be avoided in all cases where a toxin with sodium channel blocking properties may have been ingested. Seizures due to cyanide, hydrogen sulfide, and organophosphate insecticides usually require specific antidotes.

Severe agitation or prolonged convulsions can also cause rhabdomyolysis and hyperthermia. Because these complications can result in additional organ dysfunction, neuromuscular blocking agents should be given to patients who do not respond to sedatives and anticonvulsants. During such therapy, seizures should continue to be monitored (by electroencephalography) and treated to prevent permanent neurologic damage. Nondepolarizing agents are preferable to succinylcholine for inducing paralysis, because the latter agent may be hazardous in patients with rhabdomyolysis [23].

Prevention of Absorption

Early and effective decontamination can limit the surface exposure and systemic absorption of chemicals and reduce toxicity. Decontamination should be considered in all patients unless the exposure is clearly nontoxic (see Table 117.4), the time of predicted peak toxicity has passed, or the benefit of decontamination is minimal.

Body Cavity Exposure

The removal of chemicals from body cavities (e.g., bladder, external auditory canal, nose, rectum, vagina) can be accomplished by aspiration and irrigation using normal saline. Particulate matter (e.g., pills, suppositories, drug packages) should be manually removed, preferably under direct visualization. The removal of ingested drug packages from the GI tract is discussed in "Ingestion" section of this chapter.

Eye and Skin Exposure

Decontamination after topical exposure includes manual removal of particulate material, irrigation of exposed surfaces, and a scrub for skin exposure to noncorrosive chemicals. Because "time is damage," particularly with corrosives, tap water or any other readily available liquid that is clear and drinkable can be used in the prehospital setting. If exposure involves an unknown chemical, its pH should be measured. Searching for pH paper (e.g., pHydrion), usually available in the emergency department or the labor and delivery area, should not delay treatment. Irrigation should initially be performed for about 20 minutes. Prolonged irrigation (up to 24 hours) may be beneficial for corrosive exposures, especially those involving strong alkali.

With ocular exposures, blepharospasm secondary to pain can prevent effective irrigation unless treatment is preceded by the instillation of a topical anesthetic. Particulate material should be removed with a moist cotton-tipped swab or eye spud. Normal saline and lactated Ringer's solution are traditionally used irrigation fluids. It is unclear whether commercially available pH-balanced saline solutions and normal saline adjusted to a pH of 7.4 with sodium bicarbonate are less irritating than normal saline or lactated Ringer's solution [92,93]. Warming the solution may decrease discomfort [94], but this is not necessary if an anesthetic is used. Irrigating solutions can be administered via an IV infusion setup, directly through the tubing, or via an irrigating (Morgan) lens attachment. A low-pressure squeeze bottle also may be used. One or two liters is usually sufficient. For acid or alkali exposures, the tear pH (normally 7.3 to 7.7) should be determined after and before irrigation. Irrigation should continue until the pH is between 5 and 8.

For skin exposures, treatment should begin with the removal of contaminated clothing. Gloves should be worn to prevent contamination of caretakers. Particulate matter should be removed from the skin using a soft brush, forceps, or handheld vacuum cleaner before irrigation. Washing the skin with soap and water or isopropyl alcohol more effectively prevents pesticide absorption than simply rinsing with water [95]. For some toxins, a triple wash (irrigation and washing with soap before and after an alcohol scrub) may provide better decontamination than irrigation alone. Because it contains 30% alcohol, tincture of green soap has been recommended as a skin detergent [27].

Inhalational Exposure

The patient should be removed from the contaminated atmosphere and supplemental oxygen administered. Under no circumstances should a rescuer enter a hazardous dust, fume, gas, or vapor environment without adequate eye, skin, and respiratory protection.

Ingestion

GI decontamination can be accomplished with activated charcoal, gastric lavage, whole-bowel irrigation, and endoscopic or surgical removal of the ingested chemical. There is little to no role for Ipecac. Cathartics, although often used in conjunction with other treatments, are not an effective method of decontamination [96,97]. Except in cases of corrosive ingestion, the same is true for diluents.

Despite extensive experimental data documenting the efficacy of GI decontamination measures in preventing chemical absorption in animals and in human volunteers, there is no conclusive evidence that these interventions improve the outcome in actual overdose patients [98–103]. Clinical efficacy is difficult to prove because the overdose history is frequently unreliable, and most overdoses do not cause severe or life-threatening toxicity. In addition, the efficacy of GI decontamination decreases as the time between ingestion and treatment increases. Experimental data showing that GI decontamination is effective in preventing chemical absorption when initiated more than 1 hour after ingestion is limited. Since the mean time between ingestion and arrival at a hospital is more than 1 hour in children and more than 3 hours in adults [104–110], most patients present for treatment at a time when the efficacy of GI decontamination remains unknown.

With the sophisticated monitoring and supportive techniques available today, it is likely that most poisoned patients will recover fully without any decontamination therapy [105,109]. However, since experimental studies show that decontamination can limit toxin absorption and shorten the duration of toxicity, and since absorption is prolonged after overdose, decontamination may be effective longer after ingestion than experimentally proven. It is therefore recommended that it be performed unless the exposure is nontoxic (see Table 117.4), or the risk of decontamination outweighs the potential benefit.

The choice of decontamination method should be based on the relative efficacy, and contraindications of the available options. Activated charcoal has equal or greater efficacy, fewer contraindications, less frequent and less serious complications than other methods of decontamination, and is the preferred treatment for most overdoses [103–114]. Emptying the stomach via lavage is rarely indicated. Overdose patients treated with gastric lavage or syrup of ipecac in the emergency department have longer emergency department stays and have a higher incidence of pulmonary aspiration (which sometimes necessitates admission of a patient who would otherwise be discharged) than those treated with activated charcoal [104,106,107].

Gastric lavage is indicated in a recent life-threatening ingestion, when the toxin is small in size or easily dissolved in the stomach, not well adsorbed by activated charcoal and not responsive to other therapies. Syrup of ipecac is virtually never the best method of GI decontamination and is no longer routinely recommended, even for the home management of ingested poisons [115]. Whole-bowel irrigation should be considered in patients who have ingested toxic amounts of agents that are slowly absorbed or not amenable to decontamination by other techniques. Endoscopy and surgery should be reserved for patients with potentially severe poisoning in whom alternative methods of decontamination are unsuccessful or contraindicated.

Activated Charcoal. Activated charcoal can prevent absorption of ingested chemicals by binding them within the gut lumen. Its clinical efficacy remains controversial [103] because it is neither absorbed nor metabolized, the toxin bound to it is normally eliminated with stool [102,105,116,117]. Activated charcoal is a fine black powder produced by the activation (i.e., pyrolysis, oxidation, and purification) of carbon-containing materials such as bone, coal, peat, petroleum, and wood. It is odorless, tasteless, and insoluble in liquids. The activation process yields particles that have an extensive internal network of minute, branching, irregular, interconnecting channels (i.e., pores) that range in size from approximately 10 to 100 nm in diameter and account for the extremely large surface area of activated charcoal. The surface area of activated charcoal in clinical use ranges from 600 to 2,000 m^2 per g.

The absorption or adherence of chemical molecules to the external and internal surfaces of activated charcoal is rapid (within minutes of contact). It is due to relatively weak van der Waals forces and can be described by the following reversible equilibrium: activated charcoal + toxin ↔ activated charcoal – toxin complex. Hence, as the amount of activated charcoal is increased, the fraction of unbound or free chemical decreases (i.e., the equilibrium shifts to the right according to the law of mass action). At an activated charcoal to chemical ratio of 10 to 1 or greater, 90% or more of most chemicals is adsorbed into charcoal in vitro. The absorptive capacity (i.e., the amount of chemical that can be absorbed by 1 g of charcoal in vitro) ranges from a few milligrams to more than 1 g depending on the molecular size, structure, and solubility of the chemical, the pore size and surface area of activated charcoal, the negative logarithm of acid ionization constant of the chemical and the pH of the solution, and the presence or absence of competing solutes. Small, highly ionized molecules of inorganic compounds, such as acids, alkali, electrolytes (e.g., potassium), and the readily dissociable salts of arsenic, bromide, cyanide, fluoride, iron, and lithium, are not well adsorbed by activated charcoal [116,117].

In animal studies and in simulated overdoses using therapeutic or slightly greater doses in human volunteers, activated charcoal prevents the GI absorption of nearly all chemicals [116]. In agreement with in vitro studies, as the ratio of activated charcoal to chemical increases, its efficacy increases; with simultaneous dosing of activated charcoal and chemical at a ratio of 10 to 1 or greater, charcoal prevents the absorption of most chemicals by more than 90%. At a constant charcoal to chemical ratio, the efficacy of activated charcoal in preventing chemical absorption increases as the amount and concentration of either agent increases [116,117], suggesting that the efficacy of activated charcoal may be relatively greater after actual overdose than it is after a simulated one. Diluting a dose of activated charcoal and administering it in aliquots by gastric lavage is less effective than administering the same dose as a single concentrated bolus [117]. Administering a dose before and after gastric lavage is more effective than giving one only after lavage.

The interval between administration of toxin and activated charcoal also has a significant effect on the in vivo efficacy of charcoal. As this interval (i.e., the time for uninhibited absorption) increases, the ability of activated charcoal to prevent chemical absorption decreases. In controlled studies using doses of activated charcoal many times greater than those of toxin, charcoal decreased chemical absorption an average of 71% (range, 10% to 100%) when it was given within 5 minutes, 52% (range, 17% to 75%) when given at 30 minutes, and 38%, 34%, 21%, 29%, and 14% when given at 1, 2, 3, 4, and 6 hours, respectively [102,105].

The ability of activated charcoal to prevent the absorption of a toxin in vivo generally correlates with its ability to adsorb that chemical in vitro [116]. However, the absorption of some toxins that are poorly adsorbed by activated charcoal (e.g., cyanide, malathion, tolbutamide) is significantly reduced. Conversely, the absorption of some toxins that are relatively well adsorbed by activated charcoal in vitro (e.g., ethanol, ipecac, *N*-acetylcysteine) is not significantly inhibited in vivo.

The presence of food in the stomach appears to enhance the efficacy of activated charcoal in preventing the absorption of ingested agents, possibly by slowing gastric emptying. Coingested antacids, cathartics, chocolate, ethanol, and excipients have variable but relatively minor or no effect on its efficacy.

Activated charcoal is administered as an aqueous suspension; a minimum of 8 mL of water should be added to each gram of powdered charcoal if a premixed formulation is not available. Premixed product containers should be thoroughly agitated to resuspend sedimented charcoal before use.

Activated charcoal can be given orally to awake patients or by gastric tube to comatose or uncooperative patients. A nipple bottle can be used for infants. Putting the suspension in an opaque container and having the patient sip it through a straw may enhance its acceptability in adults. The recommended dose is at least 10 times the weight of the ingested toxin. Because of volume constraints, the maximum single dose is generally limited to 1 to 2 g per kg of body weight.

Compared with other methods of GI decontamination, the advantages of activated charcoal are ease of administration, rapidity of action, extensively documented safety and efficacy, lack of absolute contraindications, and its ability to enhance toxin elimination (see "Multiple-Dose Activated Charcoal" section of this chapter). The main disadvantages are its color (black), gritty taste, ability to stain clothing (which can limit its acceptance by staff and patients), and low or reversible binding of some chemicals. It can also prevent the enteral absorption and enhance elimination of drugs administered for therapeutic purposes.

In controlled studies in human volunteers, activated charcoal is equal or superior to gastric lavage and emesis in preventing drug absorption [118,119]. Activated charcoal was more effective than gastric lavage and emesis in preventing the absorption of drugs from sustained-release preparations 1 hour after drug ingestion [119] but less effective than whole-bowel irrigation at 4 hours after ingestion [120]. In awake overdose patients, activated charcoal alone caused fewer adverse effects and was equal or superior to syrup of ipecac followed by charcoal in terms of clinical outcome [107–110]. It was equally or more effective than gastric lavage followed by charcoal in obtunded patients [107,108], particularly those who presented more than 1 hour after overdose [108], although this was not observed in patients treated earlier [107]. In asymptomatic overdose patients, there was no difference in clinical outcome between those who were treated with activated charcoal and those who received no decontamination [109].

Activated charcoal is nonreactive and nonabsorbable and has little or no intrinsic toxicity. Adverse effects associated with activated charcoal therapy include nausea, vomiting, abdominal cramps, diarrhea, and constipation. These effects may be related to excessive volumes or rapid administration, concomitant cathartic therapy, prior treatment with syrup of ipecac, or the ingested toxin because they are rarely observed in volunteers given activated charcoal. Aspiration of activated charcoal along with gastric contents can result in large and small airway obstruction, pneumonitis, and death [121–124]. Aspiration of an aqueous suspension of activated charcoal can also increase airway resistance, pulmonary microvascular permeability, and shunt fraction, and decrease vital capacity [125]. If activated charcoal gets into the eyes, it can cause corneal abrasions [124].

Although there are no absolute contraindications, activated charcoal is not recommended for ingestions of acids, alkali, and hydrocarbons that are poorly absorbed and have low systemic toxicity (i.e., low-viscosity petroleum distillates and turpentine) [102,103,105,112,117]. It does not adsorb these corrosives and obscures endoscopic assessment of the extent of injury. With hydrocarbons, it may promote vomiting and increase the risk of pulmonary aspiration.

Gastric Lavage. Gastric lavage can directly remove ingested chemicals from the stomach and thereby prevent their absorption [100]. As with activated charcoal, the efficacy of gastric lavage decreases as time between ingestion and treatment increases. In animal studies and in simulated overdoses using therapeutic or slightly greater doses in human volunteers, gastric lavage decreased chemical absorption an average of 42% (range, 29% to 90%) when performed within 20 minutes of chemical administration, 26% (range, 13% to 38%) when performed at 30 minutes, and 17% (range, 8% to 32%) when performed at 60 minutes [100]. Efficacy is enhanced if activated charcoal is given before and after lavage [115], but not if it is only given afterward [118].

Gastric lavage is performed by first aspirating stomach contents and then repetitively instilling and withdrawing fluid through a nasogastric or orogastric tube [125]. It appears to be most effective if the patient is placed in a left lateral decubitus Trendelenburg position. The left lateral decubitus position has also been shown to delay spontaneous drug absorption [126]. An unknown fraction of gastric contents may enter the duodenum during gastric lavage [127]. Although theoretically reasonable and commonly stated as fact, there is no direct evidence that a large-bore tube (i.e., 28 to 40 Fr) is more effective than a small-bore (i.e., 16 to 18 Fr) tube. On the contrary, no difference in the recovery of either solid (i.e., pill) or liquid formulations with respect to tube size has been found in experimental or clinical [128] studies. Most intact pills do not fit through the lumen of even the largest tube [129]. They are, however, designed to disintegrate rapidly [127]. Hence, unless lavage is accomplished very soon after ingestion, the size of the tube is probably irrelevant.

The simplest, quickest, and least expensive method to use is a funnel connected to the lavage tube, raising it 2 to 3 feet above the level of the stomach when administering fluid and lowering it 2 to 3 feet below the stomach to allow drainage [130].

Tap water is the lavage fluid of choice for patients older than 2 years. Because of the potential for inducing fluid and electrolyte disturbances, normal saline is recommended for younger patients [131]. Using warm fluids may increase pill dissolution and inhibit gastric emptying, and massaging the epigastrium may promote the mixing and suspension of gastric contents and enhance the efficacy of gastric lavage. The optimal volume of fluid for each lavage cycle is unclear. Recommended amounts range from 60 to 800 mL for adults and up to 10 mL per kg of body weight for children [100,125,127]. Larger aliquots (5 to 10 mL per kg body weight) are superior to smaller ones. The majority of chemical recovery occurs with the initial aspiration and first few lavage cycles, but estimation of recovery on the basis of visible pill fragments in the lavage effluent is unreliable [128], probably because most of what is seen consists of insoluble excipients and bears little relation to the amount of drug present. Nevertheless, it is recommended that lavage be continued until the return is relatively clear. It is rarely necessary to use more than 5 L of fluid. Injection of air into the stomach may prevent or alleviate obstructed drainage due to mucosal collapse around lavage tube orifices. When performed successfully, the amount of fluid recovered should be 90% or more of that instilled.

Endotracheal intubation is neither necessary nor sufficient to prevent aspiration during gastric lavage. On the contrary, gastric lavage can safely be performed on awake patients without endotracheal intubation [100,131,132], and the presence of an endotracheal tube does not preclude aspiration [89,100]. In both situations, however, proper positioning is essential. In awake but uncooperative patients, it is intuitively safer to use a small-bore tube rather than a large one. The practice of physically restraining a combative patient and forcibly inserting a large-bore tube invites a mechanical complication (see later)

and should be abandoned. If a large-bore tube is deemed necessary (e.g., a witnessed ingestion of a highly lethal quantity of chemical), therapeutic sedation with or without paralysis, along with endotracheal intubation, is recommended. Short-acting agents should be used.

In experimental animal and human studies, gastric lavage is not as effective as activated charcoal [120]. In adult overdose patients, gastric lavage followed by activated charcoal was no more effective in preventing clinical deterioration than charcoal alone [104,108,110], except in comatose patients who presented within 1 hour of ingestion.

Gastric lavage can sometimes recover large amounts of chemicals. However, significant quantities of drugs are recovered in only a small fraction of patients. In acutely inebriated patients, gastric aspiration removed the equivalent of more than 40 mg per dL of ethanol in only 18% [133]. Gastric endoscopy after gastric lavage revealed residual solid in the stomach of 88% of overdose patients [134].

As in experimental studies, the clinical efficacy of gastric lavage decreases as the time between overdose and initiation of treatment increases. The efficacy of gastric lavage increases in cases of toxin induced gastroparesis or decreased intestinal motility.

Gastric lavage can result in significant morbidity and mortality. It is associated with an increased incidence of aspiration and ICU admission [104] and was thought to have contributed to death in 8 of 22 (36%) patients who died after this procedure [135]. Misplacement of the lavage tube in the trachea can result in pneumothorax, pneumonia, and death [136–138]. Malpositioning of the tube, primarily in the esophagus, has been reported in 50% of pediatric patients undergoing gastric lavage [139]. Basing tube insertion length on the child's height or length and radiographic imaging have been suggested as ways to improve and document tube placement. The lavage tube can also become kinked and impacted in the esophagus [140,141]. Because forceful removal can lead to esophageal perforation [141], inserting a flexible pediatric esophagoscope into the lumen of the tube under fluoroscopy and advancing the kinked area into the stomach where the tube can be straightened has been recommended as treatment for this complication. Esophageal spasm can prevent tube removal, a problem that can be reversed by administering glucagon [142]. Esophageal perforation can occur during tube insertion [143]. Laryngospasm [144], hypoxia, ECG changes and dysrhythmias [145], and cardiac arrest [128] have also been reported. Other complications include hematemesis, gastric rupture, charcoal empyema, and pneumoperitoneum [126,140,146,147]. On endoscopy, esophageal and gastric erosions are noted in almost all patients treated by gastric lavage using a large-bore tube [148].

Although there are no absolute contraindications to gastric lavage, its use in corrosive and hydrocarbon ingestions is rarely advisable [100,123,124,147–150]. With corrosives, insertion of a tube may increase the risk of esophageal perforation. Hence, it should be reserved for large ingestions of liquid acid or alkali and for agents that can cause systemic toxicity (e.g., heavy metals, hydrazine), and only done if it can be performed within 1 to 2 hours of exposure. Because lavage may increase the risk of pulmonary aspiration after hydrocarbon ingestion [150], it should be reserved for large ingestions of agents that have systemic toxicity (i.e., camphor, halogenated and aromatic derivatives, and those that contain heavy metals or pesticides).

Syrup of Ipecac. Although syrup of ipecac is simple to use, and was once widely available for home administration, it is less effective than activated charcoal in preventing chemical absorption in experimental studies and has more contraindications [99]. Vomiting exposes patients to aspiration risks and may preclude the administration of activated charcoal or other oral antidotes (e.g., *N*-acetylcysteine). There is virtually no role for Ipecac in the critically ill poisoned patient.

Whole-Bowel Irrigation. *Whole-bowel irrigation* refers to the enteral administration of large volumes of an electrolyte solution. It is commonly used to cleanse the GI tract before colonoscopy, barium enema radiography, and bowel surgery and can prevent the absorption of ingested chemicals by promoting enhancing gut motility [98,101,151–154].

In experimental studies, whole-bowel irrigation decreased chemical absorption by about 70% (range, 67% to 73%) when initiated 1 hour after simulated overdose of ampicillin, paraquat, and sustained-release formulations of aspirin and lithium and 4 hours after a supratherapeutic dose of enteric-coated aspirin [120,154–157]. Whole-bowel irrigation is also a form of dialysis. It has been used in the treatment of uremia [158] and can enhance elimination of previously absorbed chemicals [159]. Whole-bowel irrigation solutions have been found both to enhance [160,161] and to interfere [152–154,157] with the in vitro adsorptive capacity of activated charcoal.

Whole-bowel irrigation is performed by orally administering a solution of electrolytes and polyethylene glycol (e.g., CoLyte, GoLYTELY) at a rate of 0.5 L per hour in children 9 months to 6 years of age, 1 L per hour for 6- to 12-year-olds, and 2 L per hour for those older than 12 years, until the rectal effluent is clear, which typically takes 2 to 4 hours. In the ICU setting, the solution should be administered by nasogastric tube. The head of the bed should remain elevated during treatment.

In human volunteer studies, whole-bowel irrigation was more effective than gastric lavage and more or less effective than activated charcoal in preventing drug absorption [120,154,162]. The combination of charcoal followed by whole-bowel irrigation was more effective than whole-bowel irrigation alone but equally or less effective than charcoal alone [155–157]. Although no controlled studies addressing efficacy in overdose patients have been performed, it may be useful for ingestions of enteric-coated or sustained-release pharmaceuticals, foreign bodies (e.g., bezoars, button batteries, drug packets, lead paint chips), and agents that are poorly adsorbed by activated charcoal (e.g., iron and other metals), and in patients with extremely large ingestions or delayed presentation [102,151–174]. Potential complications of whole-bowel irrigation include regurgitation and aspiration of gastric contents and abdominal distension with cramping [102,151,156,175]. Fluid and electrolyte abnormalities have not been noted. Disadvantages of whole-bowel irrigation are that it is unpleasant, labor intensive, and time-consuming. Contraindications include bowel obstruction, perforation or ileus, and hemodynamic instability. It can be safely performed in intubated obtunded patients.

Endoscopy and Surgery. Gastric endoscopy, using baskets or snares to grasp or break up particulate chemicals, can be used to remove foreign bodies (e.g., button batteries that break apart or fail to pass beyond the pylorus) and gastric pill bezoars or concretions (see Absorption section) [176–178]. It should be reserved for patients with severe or potentially lethal poisoning, such as those with large amounts of heavy metal visible in the stomach on radiograph and those who continue to deteriorate and have rising drug levels despite attempts at GI decontamination by other methods. Endoscopy should never be used for the removal of drug packets, because it may cause rupture and lethal toxicity [179].

Immediate retrieval by laparotomy is indicated for patients who develop toxicity after the ingestion of packets containing cocaine [179]. Surgery should also be considered when

TABLE 117.11

CHEMICALS AND TOXIC SYNDROMES WITH SPECIFIC ANTIDOTES

Agent/condition	Antidotes
Acetaminophen	*N*-acetylcysteine
Anticholinergic poisoning	Physostigmine
Anticoagulants	Phytonadione (vitamin K), protamine
Benzodiazepines	Flumazenil
β-adrenergic antagonists	Glucagon, calcium salts
Calcium channel blockers	Calcium salts, glucagons
Carbon monoxide	Oxygen, hyperbaric oxygen
Cholinergic syndrome	Atropine, pralidoxime
Cyanide	Nitrites, thiosulfate, hydroxycobal
Digoxin (digitalis)	Fab antibody fragments, magnesium
Dystonic reactions	Benztropine, diphenhydramine
Ethylene glycol	Ethanol, 4-methylpyrazole, pyridoxine, thiamine
Envenomations (arthropod, snake)	Antivenins
Fluoride	Calcium and magnesium salts
Heavy metals (arsenic, mercury, lead)	British antilewisite (dimercaprol), dimercaptosuccinic acid, d-penicillamine, calcium disodium, ethylenediaminetetraacetic acid
Hydrogen sulfide	Oxygen, nitrites
Iron	Deferoxamine
Isoniazid (hydrazines)	Gamma-aminobutyric acid agonists, pyridoxine
Methanol	Ethanol, 4-methylpyrazole, folate
Methemoglobinemia	Methylene blue
Opioids	Naloxone, nalmefene, naltrexone
Sympathomimetics	Adrenergic blockers
Vacor (*N*-3-pyridylmethyl-*N′*-*p*-nitrophenylurea)	Nicotinamide (niacinamide)

endoscopic removal is unsuccessful or impossible because of the location of the toxin or foreign body [180,181].

Cathartics. Cathartics are osmotically active saccharides (e.g., mannitol, sorbitol) or salts (e.g., magnesium citrate, magnesium sulfate, disodium phosphate) that cause retention of fluids within the gut, thereby stimulating GI motility and the evacuation of intestinal contents [96,97,124,149,182–184]. In animal and human volunteer studies, cathartics have variable but clinically insignificant effects on chemical absorption [96,97]. Their effect on the efficacy of activated charcoal is also minimal and clinically insignificant [185–189]. There is currently no role for cathartics in the critically ill poisoned patient.

Dilution. The administration of water, milk, or other drinkable liquids is now recommended as a primary treatment only for corrosive ingestions [190]. In this setting, dilution may lower the concentration of chemical and limit its toxicity. To be effective, dilution should be accomplished as soon as possible. The volume of fluid should not exceed 5 mL per kg, because larger amounts may induce vomiting and cause further esophageal exposure. Dilution is no longer recommended to prevent toxin absorption. It may facilitate the dissolution of solid chemicals, increase the amount of chemical in solution, and stimulate gastric emptying, thereby enhancing chemical absorption.

Antidotal Therapy

Antidotes directly or indirectly counteract the effects of toxins [15,18,191–195]. They can be classified as *selective* or *nonselective*. Selective antidotes act by competing with chemicals for target sites or metabolic pathways, by binding and neutralizing them (e.g., antibodies and chelators), by promoting their metabolic detoxification, and by antagonizing their autonomic effects via activation or inhibition of opposing neuronal pathways (see Table 117.11). Nonselective antidotes act by correcting metabolic derangements or enhancing nonmetabolic toxin elimination.

Although antidotes can reduce morbidity and mortality, few are available and most are potentially harmful, and reasonable diagnostic certainty is necessary for their safe and effective use. Specific indications, contraindications, dosing, and potential complications are discussed in the chapters that deal with specific poisonings. A summary Table of antidotes can be found in the Appendix.

Enhancement of Elimination

The nonmetabolic elimination of most toxins can be accelerated by therapeutic interventions such as diuresis, urine alkalization, GI dialysis (i.e., multiple-dose activated charcoal or whole-bowel irrigation), and extracorporeal techniques. To be of potential clinical importance, a significant fraction (i.e., 25%) of the dose must be removed, or the rate of elimination, as assessed by clearance or half-life, must be significantly greater (i.e., 25%) than that accomplished by intrinsic mechanisms.

All enhanced elimination procedures are associated with potential complications, and some require specialized equipment and expertise. Reasonable diagnostic certainty is generally a prerequisite to their use. In general, invasive elimination procedures should be reserved for patients with severe poisoning

who deteriorate or fail to improve despite aggressive supportive care, antidotal therapy, and noninvasive methods of toxin removal [196–199].

Diuresis and Manipulation of Urinary pH

Maintenance of a dilute urine flow enhances toxin excretion by decreasing the passive distal tubular reabsorption of toxins that have undergone glomerular filtration and proximal tubular secretion [14–18,196–200]. Increasing urinary pH (considered neutral at a pH of 6) can enhance the renal excretion of acidic toxins by the mechanism known as ion trapping. Like all membranes, those of the nephron, particularly the distal tubule, are generally more permeable to nonionized and nonpolar molecules than to ionized and polar ones. After filtration and secretion, nonionized forms of weak acids or become ionized and trapped in an alkaline urine. Diuresis and urinary alkalinization act synergistically [201].

Diuresis alone can enhance the renal excretion of alcohols, bromide, calcium, fluoride, lithium, meprobamate, potassium, and isoniazid. Except for calcium and potassium, however, clinical efficacy remains unproven.

Alkalinization of the urine can enhance the excretion of the chlorophenoxy acetic acid herbicide 2,4-D (and probably 2,4,5-T), chlorpropamide, diflunisal, fluoride, methotrexate, phenobarbital (and probably other long-acting barbiturates), sulfonamides, and salicylates. Only for phenobarbital and salicylate poisoning is urinary alkalization accepted as clinically effective [202].

The goal of diuresis is a urine flow of 3 to 8 mL per kg per hour and that of alkalinization is a urine pH of 7.5 or greater. IV administration of 0.9% saline (sodium chloride) is used for inducing diuresis. An alkaline diuresis solution can be prepared by adding three ampules (132 mEq) of sodium bicarbonate to dextrose 5% in water such that the final solution is nearly isotonic. Fluids are administered roughly at the same rate as the desired urine output. Acetazolamide should not be used to produce an alkaline urine, because it may worsen toxicity by causing a concomitant systemic acidosis, resulting in an increase in the amount of unionized drug in the blood and enhanced tissue distribution [203]. It may also compete with acidic drugs for tubular secretion and thereby inhibit their elimination.

Acid–base status, fluid balance, electrolyte parameters, and clinical response must be carefully monitored during therapy. Urine pH should be measured hourly.

Multiple-Dose Activated Charcoal

Repetitive activated charcoal administration can enhance the elimination of previously absorbed chemicals by binding them within the GI tract as they are excreted in the bile, secreted by cells of the stomach or intestine, or passively diffuse into the lumen of the gut [116,204–206]. The charcoal–chemical complex is then excreted with stool. In most cases, reverse absorption (enterocapillary exsorption) is the mechanism, with the entire surface of the gut acting as a dialysis membrane. Activated charcoal keeps the concentration of free toxin in gut fluids near zero, and chemicals merely diffuse from blood perfusing the gut into luminal fluids as a result of concentration gradients. Interruption of enterohepatic or enteroenteric recirculation appears to be the underlying mechanism of action for a minority of toxins. Theoretically, multiple-dose charcoal can enhance the elimination of any chemical whose absorption is decreased by a single dose. Efficacy is predicted to be greatest for chemicals with a high charcoal binding capacity, physical and pharmacokinetic characteristics that make them amenable to removal by extracorporeal methods (see later), and a long intrinsic elimination half-life (e.g., amiodarone, isotretinoin, organochlorine pesticides, organometallic compounds) [207].

Multiple-dose activated charcoal enhances the elimination of most chemicals regardless of whether the chemical is administered orally or parenterally [206]. As with most forms of decontamination, the clinical efficacy of this therapy remains unproven [208]. Although clinically significant reductions in half-life have been noted in patients with carbamazepine, dapsone, phenobarbital, quinine, and theophylline overdose, there are no prospective studies showing that this therapy reduces morbidity or mortality [206].

The efficacy of multiple-dose activated charcoal increases as the cumulative amount of charcoal administered increases, either by increasing the amount or frequency of charcoal dosing [209]. When the cumulative amount of charcoal remains constant, there is no difference in the efficacy of different dosing regimens (e.g., 25 g every 2 hours vs. 50 g every 4 hours) [210]. With normal bowel activity, doses of activated charcoal of 0.5 to 1.0 g per kg every 4 hours are generally well tolerated. In those with decreased GI motility, smaller doses or less frequent intervals should be used. Alternatively, charcoal can be given by a slow, continuous nasogastric infusion. This method of administration may also be better for patients who cannot retain charcoal because of vomiting. Metoclopramide and odansetron (or other serotonergic antiemetics) can also be given to control or prevent vomiting. Gastric aspiration should be performed before repeating the dose of charcoal. In the event of gastrostaxis, regurgitation, or abdominal distension, treatment should be withheld.

Complications of multiple-dose activated charcoal are similar to those for charcoal used for GI decontamination. In addition, intestinal obstruction, pseudo-obstruction, and nonocclusive intestinal infarction have been reported in patients with decreased bowel motility treated with multiple doses of activated charcoal [211–215].

Extracorporeal Methods

Peritoneal dialysis, hemodialysis, hemoperfusion, hemofiltration, plasmapheresis, and exchange transfusion are theoretically capable of removing any chemical from the blood [210,216–222]. There remains very little evidence regarding the efficacy of continuous renal replacement therapy in the management of human poisonings. Most toxins undergo significant tissue distribution, and few remain in the blood in amounts high enough to warrant extracorporeal removal. Hemodialysis is therefore most effective for toxins with volumes of distribution less than 1 L per kg. In addition, with dialysis techniques, only toxins that are small (i.e., molecular weight less than 500 to 1,500 Da), water soluble, uncharged, and not highly bound to serum proteins (90% to 95% or less) readily diffuse across dialysis membranes. (Table 117.12)

The clearance of a toxin by extracorporeal removal must be significantly greater than its intrinsic total body clearance (i.e., the sum of metabolic, renal, and other routes of clearance) to be considered effective from a pharmacokinetic perspective. As with other treatments, their clinical efficacy (i.e., ability to decrease morbidity and mortality) is based on observation, experience, and retrospective comparisons rather than on controlled prospective studies.

Hemodialysis is considered effective for the treatment of barbiturate, bromide, chloral hydrate, ethanol, ethylene glycol, isopropyl alcohol, lithium, methanol, procainamide, acetaminophen, theophylline, salicylate, and possibly heavy metal poisoning [196–198]. Because hemodialysis can remove toxins from the blood faster than they can redistribute from tissue to blood, a rebound increase in blood concentration and clinical relapse may occur within 1 or 2 hours of treatment.

Other techniques are less effective than hemodialysis. Peritoneal dialysis may be useful when these methods are not

TABLE 117.12

PROPERTIES OF A DIALYZABLE TOXIN

1. Small volume of distribution
2. Low molecular weight
3. Water soluble
4. Uncharged
5. Low protein binding

available or technically difficult (e.g., in neonates) or when anticoagulation may be hazardous [197,198]. Complications include infection, injury to intra-abdominal organs, and hypothermia. Plasma exchange may also be a useful alternative in neonates. It is effective for treating hemolysis (e.g., arsine poisoning) and methemoglobinemia. Two blood-volume exchanges are usually performed using central or peripheral arteriovenous or venovenous access. Complications include transfusion reactions and hypothermia. The roles of hemofiltration and plasmapheresis in the treatment of poisoning remain to be defined [219–222].

Safe Disposition

ICU admission is recommended for patients with coma, refractory hemodynamic instability, respiratory depression, seizures, and/or dysrhythmias [223,224]. Patients with extremes of temperature, severe agitation, or life-threatening metabolic abnormalities also benefit from intensive care. CNS depression may be the best predictor of serious complications [7]. Patients who are less ill, stable, or even asymptomatic are frequently unnecessarily admitted to the ICU because of physician uncertainty, fear of late deterioration and potential litigation, and lack of an alternative monitored setting. Some patients may require close observation and cardiac monitoring; but unless active interventions are likely to be necessary, admission to an intermediate care unit, telemetry unit, or emergency department observation unit is adequate. Length of hospital stay in patients with self-poisoning can be reduced by use of a multidisciplinary team that involves a toxicologist and psychiatrist as well as medical personnel [225].

Prevention of Recurrence

Suicidal patients require psychiatric assessment. If they are given prescriptions, the amount of drug (e.g., a 1- to 2-week supply) and number of refills should be limited. Substance abusers should be counseled regarding attendant medical risks and given the opportunity for rehabilitation through referral for behavior modification, supervised withdrawal, and abstinence or maintenance therapy.

Adults with accidental poisoning should be educated regarding the safe use of drugs and other chemicals. Assistance with the administration of medications may be required for visually impaired, elderly, developmentally delayed, or confused patients. Preventive education may be indicated for health care providers who have committed dosing errors or who are unaware of adverse drug interactions. When poisoning results from environmental or workplace exposure, the appropriate governmental agency (e.g., Environmental Protection Agency; Occupational Safety and Health Administration; National Institute of Occupational Safety and Health; or local, state, or federal health departments) should be notified. Unsafe working conditions should be brought to the attention of employers. Industrial hygiene and occupational health services should be offered if available. Finally, physicians have a duty to warn the general public (e.g., via press releases) of acute environmental hazard.

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CHAPTER 118 ■ ACETAMINOPHEN POISONING

STEVEN B. BIRD

PHARMACOLOGY

Acetaminophen (*N*-acetyl-para-aminophenol [APAP]) is a nonnarcotic analgesic with excellent antipyretic activity but almost no anti-inflammatory effects. It belongs to the same drug family as phenacetin and acetanilid, the coal tar or aminobenzene analgesics [1,2]. Although APAP is the active metabolite of phenacetin, unlike phenacetin it rarely, if ever, causes nephrotoxicity and does not cause methemoglobinemia and hemolytic anemia. Unlike aspirin, APAP has no barrier-breaker effect on the gastrointestinal tract and no effect on platelet function, has a high therapeutic index, and has not been implicated as a factor in Reye's syndrome. As a result, APAP is the preferred agent

for the treatment of fever and mild to moderate pain when anti-inflammatory and antiplatelet action is not important.

Acetaminophen is an active ingredient in several hundred products, including pure APAP formulations, combinations with opioid analgesics, and numerous combination cough and cold preparations. It is also available in an extended-release (ER) formulation (which contains 325 mg of immediate-release and 325 mg of delayed-release acetaminophen per tablet) and as a suppository, but there is no commercial intravenous formulation.

Acetaminophen has a pK_a of 9.5 and is quickly and almost completely absorbed after ingestion of therapeutic doses of immediate-release formulations (10 to 15 mg per kg every 4 hours), yielding peak plasma concentrations between 5 and 20 µg per mL within 30 to 120 minutes. Clinical effects are noted within 30 minutes. Liquid preparations are absorbed slightly faster than solid formulations. Rectal absorption is similar to that of oral ingestion. The volume of distribution of APAP is 0.9 to 1.0 L per kg, and protein binding is negligible. Therapeutic plasma concentrations range from 10 to 20 µg per L, and elimination after therapeutic dosing follows first-order kinetics, with an average half-life of 2 to 4 hours [1]. Elimination is slower in neonates and young infants [3], the elderly [2], and in patients with hepatic dysfunction [4]. Clinical effects persist for 3 to 4 hours after therapeutic doses.

After overdose, peak acetaminophen levels are usually noted within 4 hours. The ingestion of very large doses and the concomitant ingestion of agents that delay gastric emptying (e.g., anticholinergics and opioids) may result in peak levels occurring later. Prolonged absorption with a late rise in the acetaminophen level has also been reported after an ER overdose [5].

TOXICOLOGY

The short- or long-term therapeutic use of APAP is rarely associated with adverse effects. Hypersensitivity reactions, such as urticaria, fixed drug eruption, angioedema, laryngeal edema, and anaphylaxis, are extremely rare [6]. Although high-dose APAP has been associated with chronic renal impairment [7], a cause-effect relationship has not been established.

Despite remarkable safety in appropriate doses, APAP can cause fatal hepatic necrosis after overdosage. This was first recognized in Europe more than 40 years ago and the first cases of hepatotoxicity in the United States were reported in 1975. Since that time, the incidence of APAP poisoning has increased dramatically in parallel with its increased availability and use; APAP is now the most common drug involved in exposures reported to US poison control centers, accounting for more than 140,000 calls in 2007 [8]. The incidence of occult poisoning is unknown, but based on retrospective data approximately 1 of every 70 overdose patients have a detectable acetaminophen concentration and 1 in 500 a potentially toxic APAP ingestion [9].

The metabolism of APAP explains its toxicity and the rationale for the current treatment of overdose (Fig. 118.1) (Table 118.1) [2]. After therapeutic doses, approximately 90% of APAP metabolism occurs by hepatic conjugation with sulfate or glucuronide to form inactive, nontoxic, renally eliminated metabolites. In adults, glucuronidation is the predominant route; in infants and young children, sulfation is the major pathway. Less than 5% of APAP is eliminated unchanged in the urine. The small remaining fraction (approximately 5%) undergoes oxidation by the P450 mixed-function oxidase enzyme system (CYP2E1) to yield the highly reactive, potentially toxic, electrophilic intermediate *N*-acetyl-para-benzoquinoneimine (NAPQI) [10]. NAPQI is quickly detoxified by reduced glutathione (GSH) to form nontoxic cysteine and mercapturic acid conjugates that are excreted in the urine.

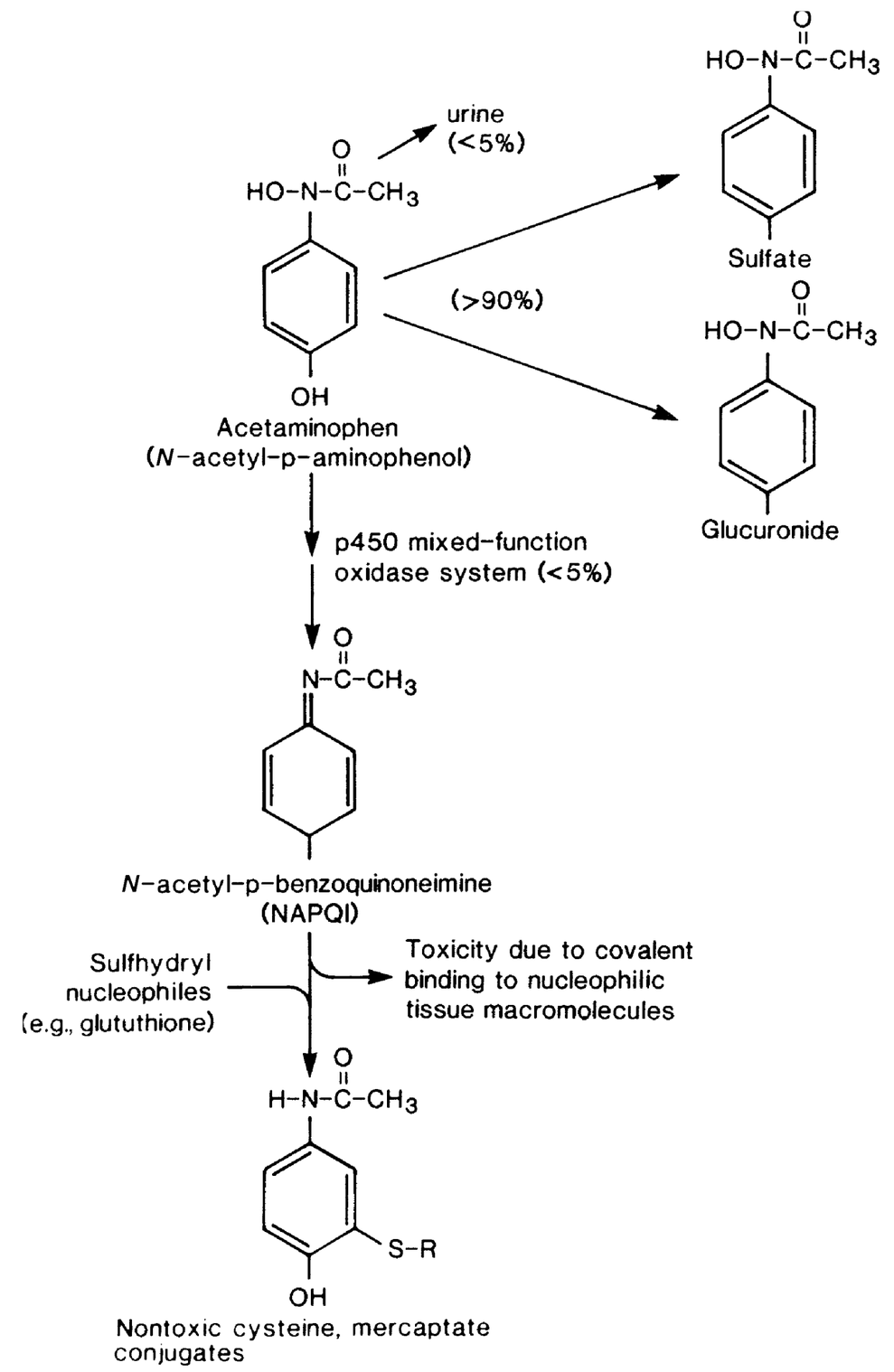

FIGURE 118.1. Postulated metabolism of acetaminophen. Toxicity occurs when the supply of sulfhydryl nucleophiles (e.g., glutathione) is inadequate to prevent the persistence of *N*-acetyl-para-benzoquinoneimine (NAPQI) and subsequent binding to hepatocyte macromolecules.

After overdose, the amount of drug metabolized by the P450 route increases, because of a greater total drug burden and saturation of alternative enzymatic pathways [11]. As a result, GSH utilization increases. If GSH regeneration is inadequate to meet demand and becomes significantly depleted, NAPQI can persist and react with hepatocyte macromolecules, resulting in the death of hepatocytes. In animal studies, such injury occurs when GSH stores reach less than 30% of normal [12]. Hepatocyte necrosis is most pronounced in areas of highest CYP2E1 activity: the centrilobular (central venule) zones of the liver. The degree of injury can range from asymptomatic

TABLE 118.1

TREATMENT OF ACETAMINOPHEN POISONING OR ASSOCIATED HEPATOTOXICITY

1. Administer activated charcoal if ingestion within 1–2 hours
2. Administer NAC either IV (preferred) or orally
3. Early consultation with hepatology and or transplant services for critically ill patients
4. Psychiatric evaluation for all intentional overdoses

elevations in aminotransferase levels to fulminant liver failure. Although far less common, the same process can occur in the kidney [13]. Very rarely, renal toxicity can occur in the absence of serious hepatotoxicity [14].

Pancreatitis, in some cases fulminant, can occur, and diffuse myocardial necrosis has been noted in fatal cases. Very rarely, with massive ingestions, early coma and metabolic acidosis may be seen [15]. Although uncommon, thrombocytopenia after acute overdose has also been described [16]. The mechanisms causing these atypical toxicities are unknown, and it is unclear to what extent these effects are directly due to APAP.

The precise dosage required to produce hepatotoxicity is unknown and almost certainly varies to some degree with individual differences in CYP2E1 activity, GSH stores, and capacity for GSH regeneration. Retrospective data suggest that significant toxicity is likely only after acute overdoses of greater than 250 mg per kg in adults [13], and prospective studies have suggested that toxicity is unlikely in unintentional pediatric ingestions of up to 200 mg per kg [17]. The possibility of toxicity at lower doses and skepticism regarding the accuracy of overdose histories have led to acceptance of a more conservative definition of risk, particularly in the United States. On the basis of APAP's volume of distribution and the well-established accuracy of APAP blood levels in predicting toxicity (see later), it is currently recommended that single ingestions of greater than 140 to 150 mg per kg be considered potentially toxic.

Elevated aminotransferase concentrations have also been reported after repeated ingestions of therapeutic or slightly greater doses of APAP [18]. Individuals who have conditions associated with increased CYP2E1 activity (e.g., chronic alcoholics) or glutathione depletion such as children younger than 10 years of age [19], those with chronic malnutrition, recent fasting (due to intercurrent illness), or recent ethanol use [20] may be at increased risk for such toxicity, but the accuracy of these reports has been challenged, and their therapeutic implications remain controversial. Such individuals are likely to have low hepatic carbohydrate and sulfate stores and, hence, decreased capacity for APAP metabolism via the glucuronidation and sulfation. There is currently no valid estimation of the amount, frequency, or duration of the dosing that defines risk. It appears that after repeated doses, accumulation of APAP to concentrations associated with toxicity after acute overdose is not required and that sustained moderate elevations are sufficient to cause GSH depletion and toxicity [21]. Such observations suggest that the APAP level at which NAPQI production exceeds GSH regeneration is near, or possibly within, the therapeutic range and that GSH stores and the capacity for its regeneration are the most important factors in the development of hepatotoxicity. They also support the concept that hepatotoxicity is more dependent on the area under the curve (time vs. concentration) of APAP than the peak drug level.

Intentional acute overdose is the most common cause of toxicity and fatalities, but accidental therapeutic overdosing and the abuse of opioids with unintentional coingestion of APAP (e.g., with codeine or propoxyphene) have also been reported. Therapeutic overdoses may result from dosing calculation errors, excessive self-treatment, the use of adult formulations or extra-strength formulations when lower dosage formulations were intended, and errors involving substitution of higher-dose rectal suppositories for similar-appearing lower dosage forms.

The importance of accurately diagnosing APAP toxicity soon after overdose extends beyond the high frequency with which it is encountered and its potential for causing morbidity and mortality. Acetaminophen is unique among common toxic exposures because effective treatment requires recognition of potential poisoning and initiation of therapy when no reliable clinical signs of overdose are present. Physicians must therefore consider occult APAP ingestion and liberally obtain APAP levels on all overdose patients to avoid missing the diagnosis.

CLINICAL MANIFESTATIONS

Acetaminophen hepatotoxicity can be divided into four clinical stages based on the time interval after ingestion: stage I (0 to 24 hours), the latent period; stage II (24 to 48 hours), the onset of hepatotoxicity; stage III (72 to 96 hours), maximal hepatic injury; and stage IV (4 days to 2 weeks), recovery [2,13].

During stage I, patients may be completely asymptomatic but often experience nausea, vomiting, and malaise, which may be accompanied by pallor and mild diaphoresis. There is no known correlation between presence or absence of early symptoms and the risk of hepatotoxicity. Although late in stage I very sensitive indicators of hepatic injury, such as γ -glutamyltransferase level, may be elevated, more widely used laboratory studies (e.g., aspartate aminotransferase [AST], alanine aminotransferase, prothrombin time, bilirubin) are completely normal. Early coma and metabolic acidosis have been reported in patients with massive ingestions [15], but these findings are so atypical that other causes should be suspected. They should be attributed to APAP only if the APAP concentration is extremely high and other etiologies have been excluded.

Symptoms during stage II are typical of hepatitis and include right upper-quadrant abdominal pain, nausea, fatigue, and malaise. Physical examination often reveals right upper-quadrant tenderness and hepatomegaly. The first elevation of aminotransferase levels usually occurs between 24 and 36 hours after APAP ingestion, but in the most severe cases, it can occur by 16 hours or earlier. Early in stage II, tests reflecting liver function, such as bilirubin and prothrombin time, are most often normal or only slightly elevated. Marked elevations of aminotransferase levels (greater than 1,000 IU per L) within 24 hours or bilirubin and prothrombin time within 36 hours should suggest that the time of ingestion was earlier than reported. Although unusual, in severe cases, marked liver function abnormalities may be evident by 36 to 48 hours. Complications during stage II are directly related to the degree of liver injury and may include coagulopathy, encephalopathy, acidosis, and hypoglycemia. With few exceptions, life-threatening problems are not seen earlier than 48 hours, and death in this period is distinctly rare. Renal dysfunction, manifested by rising creatinine and an active urinary sediment, may become evident during this stage but usually lags somewhat behind the hepatic injury. The blood urea nitrogen may also be elevated, but it can be normal in the presence of hepatic failure and resultant decreased urea formation.

Biochemical evidence of liver injury becomes most pronounced during stage III. With successful treatment, however, peak aminotransferase levels may sometimes occur earlier (Fig. 118.2). Most patients, even those with markedly elevated aminotransferase levels, go on to recover fully. Most deaths occur 3 to 7 days after ingestion and result from intractable metabolic disturbances, secondary complications such as cerebral edema or dysrhythmias, or exsanguination due to coagulopathy. Oliguric or anuric renal failure may result from acute tubular necrosis and is sometimes accompanied by flank pain. Some degree of renal dysfunction occurs in approximately 25% of patients with significant hepatotoxicity [15]. Even when severe, renal failure is almost always reversible.

During stage IV, if sufficient hepatocytes remain viable and the patient survives, the liver regenerates. Recovery is often complete by day 5 or 6 in patients with minimal toxicity, but those with more serious poisoning may not be clinically normal for 2 weeks or more. It is interesting that even patients with severe toxicity who survive regain normal liver function. There are no known cases of chronic or persistent liver abnormalities from APAP poisoning. In those who ultimately die, a slow decline in aminotransferase levels without clinical improvement may be seen. Declining enzyme levels merely

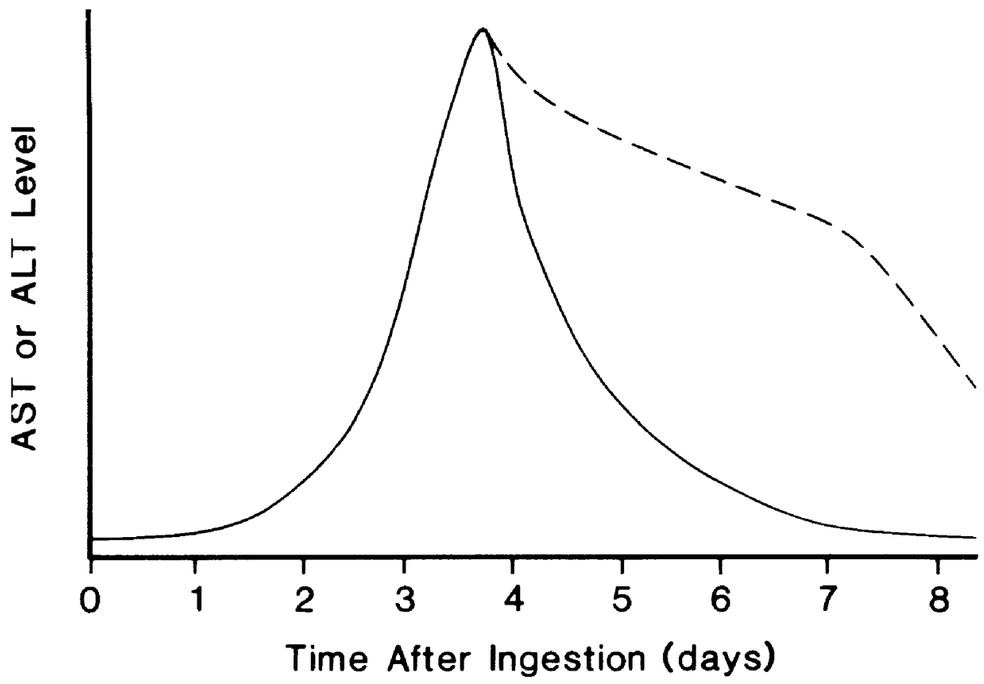

FIGURE 118.2. Expected time course of aminotransferase elevation due to acetaminophen-induced hepatotoxicity. The solid line represents typical course; the dashed line represents course of severe toxicity. ALT, alanine aminotransferase; AST, aspartate aminotransferase [Adapted from Jaeschke H, Mitchell JR: Neutrophil accumulation exacerbates acetaminophen-induced liver injury (abstract). *FASEB J* 3:A920, 1989, with permission.]

represent a washout of those released at the time of the initial insult, not a recovery of normal liver function. These patients can be identified by persistent or increasing marked elevations of bilirubin and prothrombin time. Although this pattern is occasionally seen in patients who recover, most survivors do not have significant or persistent bilirubin or prothrombin time elevation after aminotransferase levels fall.

Because of variations in dosing patterns and patient characteristics, the time course of toxicity in patients with repeated ingestions is not well defined. With chronic toxicity, dose–response patterns differ from those of acute overdose, but the clinical manifestations are the same.

DIAGNOSTIC EVALUATION

The diagnostic evaluation consists of determining the risk of toxicity and assessing for it. The serum APAP concentration is used to predict toxicity after acute overdose. If the APAP concentration between 4 and 24 hours after ingestion falls on or above the acetaminophen treatment nomogram line (Fig. 118.3), the patient should be considered at risk for hepatotoxicity, and hence, in need of antidotal therapy (see later). Conversely, if the APAP concentration is even slightly below the nomogram line, the risk of hepatotoxicity is negligible and antidotal therapy is not necessary. The original Rumack–Matthew nomogram line, which defined the risk of toxicity based on the natural course of untreated patients [22], was actually 25% higher than the line now used in the United States. Hence, the nomogram has a 25% safety margin that allows one to be fairly rigid when using the nomogram to make treatment decisions.

There are, however, some important caveats regarding use of the nomogram. First and foremost, it applies only to single acute ingestions. Second, when there is uncertainty about the exact time of ingestion, the worst-case scenario should be assumed. For example, if the ingestion was between 4 and 6 hours earlier, the 6-hour value on the nomogram should be used. And finally, when levels are obtained 20 to 24 hours after overdose, the limit of detection of the APAP assay must also be considered. Because most hospitals use immunoassays with a detection limit of 10 µg per mL, potentially toxic APAP levels during this period will be below this limit and reported as nondetectable, which does not necessarily mean nontoxic. Again,

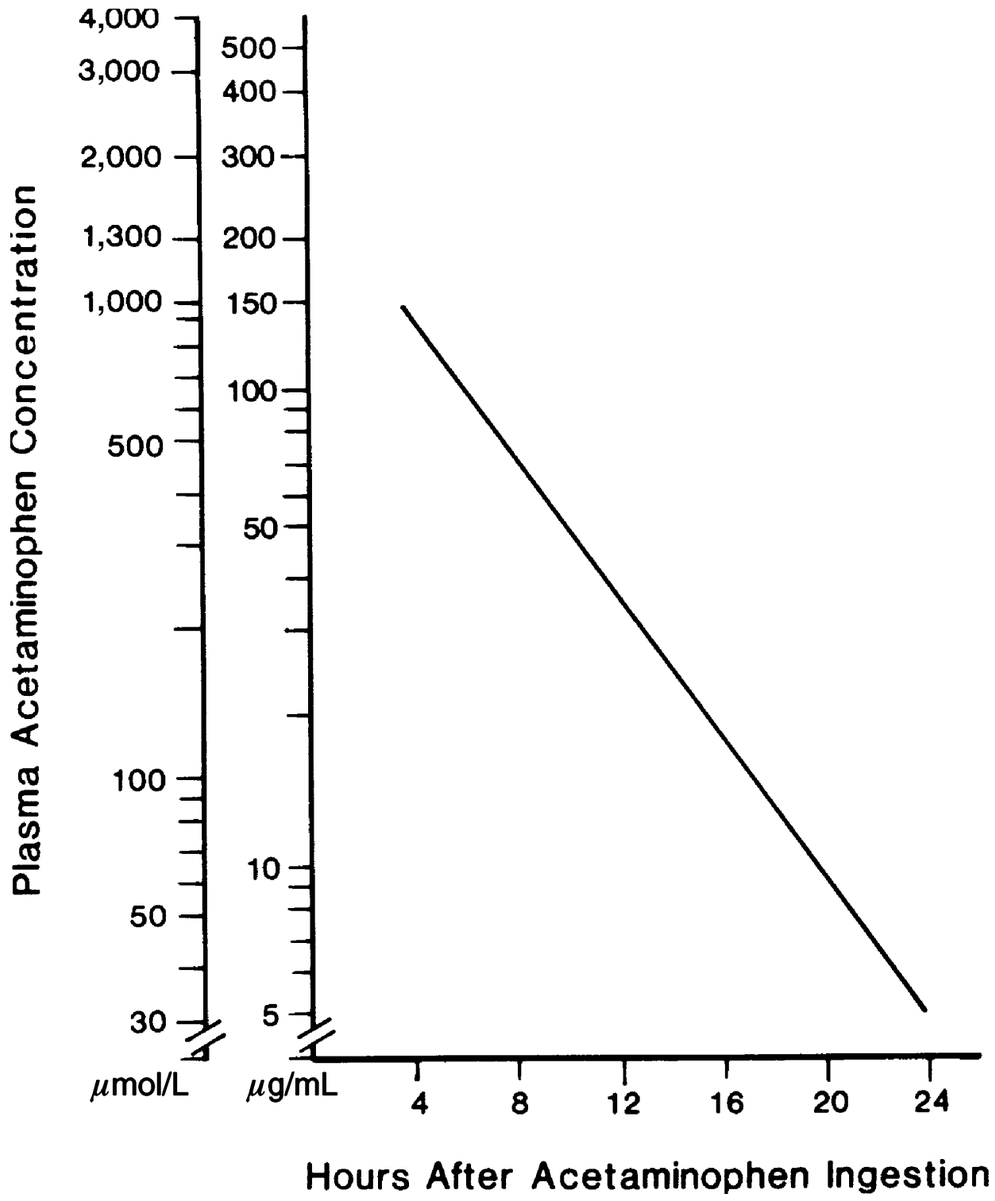

FIGURE 118.3. Acetaminophen treatment nomogram. Patients with acetaminophen concentrations on or above the line require treatment with *N*-acetylcysteine. [Adapted from Jaeschke H, Mitchell JR: Neutrophil accumulation exacerbates acetaminophen-induced liver injury (abstract). *FASEB J* 3:A920, 1989, with permission.]

a worst-case scenario should be assumed, and antidotal treatment should be given until the level is confirmed to be nontoxic by a more sensitive assay, or until it has been determined that the patient is asymptomatic and has no laboratory evidence of hepatotoxicity.

With rare exceptions (see later), a single APAP concentration within the time period specified by the nomogram is sufficient to plan appropriate therapy. Although it is true that the elimination half-life of APAP is related to the likelihood of toxicity, half-lives should not be relied on in making therapeutic decisions. The observations that half-lives greater than 4 hours were associated with toxicity and that toxicity was negligible if APAP half-life was less than 4 hours [23] were based on multiple APAP determinations in untreated patients over a 36-hour period. Because treatment must be started as early as possible [24] and treatment may alter APAP elimination [11], half-life determinations are not relevant to current standards of care.

There are three situations in which repeat measurements may be of value. The first is in the patient with a time of ingestion that is unknown but that was within 4 hours. In this situation, an increasing APAP level indicates ongoing absorption from a recent ingestion. To detect a rising level and define the peak value, repeat determinations must be frequent (every hour) until the level declines. This prevents underestimation of the peak value due to incomplete absorption at the time of the first level. It also may rule out toxicity by detecting a peak value less than 150 µg per mL.

The second situation in which repeating the APAP may be useful is after an overdose of an ER formula. Because of prolonged absorption, patients with nontoxic APAP levels soon after ingestion may have subsequent levels that are toxic by the nomogram [25]. The optimal time to repeat drug levels to detect such nomogram line-crossers is unknown. In one patient, a

potentially toxic APAP level did not occur until 14 hours after ingestion [5]. The manufacturer recommends obtaining a second APAP level 4 to 6 hours after the initial one [26]. Others have recommended that to avoid missing a potentially toxic level, drug levels should be measured every 2 hours from 4 to 16 hours after overdose [27].

Finally, repeat APAP levels may be of value in the patient with very high levels and slow elimination in whom it is possible that APAP may still be present at the completion of therapy. Antidotal treatment should not be discontinued while APAP is still present. This is particularly relevant as shorter courses of antidotal therapy have become the routine.

In assessing the patient who is found to be at risk for toxicity and hence requires hospitalization and antidotal treatment, a complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, prothrombin time, aminotransferase levels, and bilirubin should be obtained at admission and repeated every 24 hours until resolution of toxicity is noted. If liver failure develops, laboratory values, particularly prothrombin time and glucose, must be obtained more frequently. Renal function, acid–base status, amylase, and electrocardiogram may also need to be evaluated or repeated. Assessment of renal, pancreatic, and myocardial toxicity should follow the same guidelines as those for other etiologies.

MANAGEMENT

Treatment includes gastrointestinal decontamination, antidotal treatment (if indicated), and support of organ function. Unless clinically significant hepatic or renal failure develops, management consists only of antidote administration and monitoring of signs, symptoms, and laboratory parameters. Although this can be accomplished outside the intensive care unit, patients often require monitoring or treatment for toxicity due to coingestions or constant observation because of suicide risk. If significant hepatic failure ensues, intensive care unit admission is required for close monitoring and treatment of complications. Invasive monitoring is infrequently required, but may be useful if multisystem failure occurs.

Gastrointestinal Decontamination

Gastrointestinal decontamination is recommended for patients who can be treated within 1–2 hours of APAP overdose. Although once considered controversial and even contraindicated, activated charcoal is now considered the method of choice. As routine treatment of APAP poisoning has moved from oral *N*-acetylcysteine (NAC) to intravenous administration, this formerly contentious point has been rendered moot.

Antidotal Treatment

The observation that hepatotoxicity occurs only when GSH is depleted led to a search for agents that might increase available sulfhydryl groups either by increasing GSH or by providing alternative sulfhydryl sources. Exogenous GSH does not readily enter cells, so various precursors and substitutes, including cysteamine, methionine, and NAC [24,28], have been tried. Although all regimens are effective when started within 8 to 10 hours of ingestion, cysteamine was abandoned because of its toxicity, and methionine has been replaced by NAC, which is more effective and probably carries less risk of worsening hepatic encephalopathy when liver failure is present.

There are several suggested mechanisms of action of NAC. In cells, NAC is converted to cysteine, a GSH precursor, and thus increases GSH stores. Second, NAC or cysteine can substitute directly for GSH because it has available sulfhydryl groups. Third, NAC augments the sulfation of APAP to nontoxic metabolite by providing sulfur substrate [11]. Fourth, NAC may promote the back conversion of NAPQI to its precursors, although this has not been demonstrated in humans. Finally, there is accumulating evidence that NAC may be beneficial, even after liver injury has occurred, through mechanisms other than its effects on APAP metabolism [29]. Suggested mechanisms for these late effects of NAC include direct antioxidant action to modify postinflammatory radical-mediated destruction, restoration of enzyme function in injured tissue, and correction of microvascular function by restoring endothelial-derived relaxing factor [29]. It is likely that the relative importance of each of the previously described effects of NAC in any given patient varies with the severity of the overdose and the delay to NAC initiation. These variations may explain apparent differences in efficacy between different NAC protocols.

Two treatment regimens are currently approved for use in the United States. The first consists of a 72-hour course of oral NAC given as a 140 mg per kg loading dose, followed by 17 doses of 70 mg per kg every 4 hours beginning 4 hours after the loading dose, for a total NAC dose of 1,330 mg per kg [30]. The second regimen, approved by the FDA in 2004, consists of an intravenous loading dose of acetylcysteine of 150 mg per kg in 200 mL dextrose 5% in water (D_5W) over 15 minutes, followed by 50 mg per kg in 500 mL D_5W over 4 hours, then 100 mg per kg in 1 L D_5W over the next 16 hours [31]. This is identical to the standard treatment regimens in Europe and Canada [28]. Because the FDA-approved dosing requires three separate intravenous formulations, some Poison Control Centers, hospitals, and medical toxicologists have simplified NAC protocols that differ from the FDA-approved dosing [32].

For oral therapy, NAC is usually supplied as a 20% solution (20 g per 100 mL), which should be diluted 3 to 1 to yield a 5% mixture with juice or a soft drink to increase its palatability and decrease gastrointestinal side effects. Antiemetics (e.g., metoclopramide, 0.1 to 1.0 mg per kg intravenous (IV), initial adult dose 10 mg; droperidol, 20 to 150 µg per kg IV, initial adult dose 1.25 mg) may be required to treat antecedent vomiting or vomiting due to NAC. Ondansetron (50 to 150 µg per kg IV, initial adult dose 4 mg) may be effective when traditional antiemetics are not. If antiemetics fail, NAC can be given by gastric or duodenal tube. Various other methods may prove helpful in decreasing emesis after dosing: chilling the solution with ice chips, using a straw and covering the container, diluting to a 10% solution, or administering the solution over 15 to 60 minutes instead of as a bolus. If vomiting occurs within 1 hour of any dose, that dose should be repeated.

The use of oral or IV NAC is dependent on the experience of the clinician, the local hospital formulary, severity of the patient, and physician preference. Most patients can be adequately treated with oral NAC if it is begun within 8 to 10 hours of ingestion. Other patients, particularly those who present after 8 to 10 hours or those with encephalopathy, should receive IV NAC therapy.

There are no well-documented serious side effects of oral NAC, although nausea and vomiting are extremely common [33]. Side effects from intravenous NAC are far less common but potentially more serious. There are several reports of serious or fatal anaphylactoid reactions (e.g., hypotension, bronchospasm, rash, death) to intravenous NAC during the 20-hour protocol, and minor dermatologic reactions are common [34,35]. It is important to recognize that adverse effects to intravenous NAC are not truly anaphylactic; they are dose and concentration dependent [34]. As a result, more dilute and slowly administered doses are better tolerated [36]. Except for an anaphylactoid reaction in one patient after an NAC overdose, there were no serious adverse reactions reported during

the 48-hour intravenous protocol [36]. Transient skin rash occurred in approximately 15% of patients during the loading dose but did not necessitate discontinuing treatment. Even with more serious reactions, NAC therapy can often be continued or resumed after treatment with diphenhydramine [35].

All dosing protocols appear to be equivalent when NAC is started within 8 hours of ingestion. Efficacy decreases with longer delays in therapy, with apparent differences between the dosing regimens when NAC is started after 16 hours. With late treatment, 82% of high-risk patients treated with the 20-hour regimen developed aminotransferase values above 1,000 IU per L, an incidence not significantly different from the 89% incidence reported in untreated historical control subjects [28]. After treatment with 48 hours of intravenous NAC, only 58% of late-treated patients developed hepatotoxicity, a result that was significantly better than that with the 20-hour course or no treatment [36]. After 72 hours of oral NAC, only 41% of late-treated patients developed hepatotoxicity [24], although this was not statistically different from the 48-hour protocol [36]. These studies included only patients receiving NAC within 24 hours of ingestion.

In the first controlled study of NAC started more than 24 hours after overdose, intravenous NAC started after onset of liver failure (median 53 hours after APAP) reduced cerebral edema, need for pressors, and mortality [37]. It is interesting that this study used the same NAC dosing that had earlier been found ineffective more than 15 hours after overdose [28], but instead of discontinuing NAC after 20 hours, therapy was continued until either recovery or death occurred.

The numerous actions of NAC may explain why various NAC protocols are equivalent when started early but not when started late. When started within 8 hours of overdose, NAC probably exclusively affects APAP metabolism and GSH turnover, and its role is preventative before GSH depletion and NAPQI covalent binding. In this setting, NAC may be needed only until APAP metabolism is complete; thus, shorter courses of NAC are effective. With further treatment delay, the role of NAC may increasingly be to ameliorate the effects of NAPQI covalent binding, and by 16 hours after ingestion, this may be its sole action and would explain why longer courses of NAC, continued during the period of maximal liver injury, appear to be superior. These considerations have led to selective management, such as short-course NAC for those treated early who do not develop aminotransferase elevations or late treatment with NAC for any patient who develops liver injury (see later).

Cimetidine has been suggested as a possible antidote for APAP because of its inhibitory effect on P450 activity. Animal studies showed efficacy of high-dose cimetidine given before or soon after APAP, but there is no evidence of efficacy in humans [38]. Even if the massive dose suggested by animal studies proved to be safe and effective in humans, its theoretic effect would require early administration. In problematic cases, such as late presentation, there is no theoretic or experimental support for cimetidine use. Hence, although cimetidine is not contraindicated, it has no proven role and should never be considered an alternative to NAC.

Supportive Care

The management of hepatic failure, renal failure, or other end-organ manifestations of APAP toxicity should be treated according to usual guidelines. In view of the increased availability and success of liver transplantation, the most severely ill patients deserve this consideration. Several successful transplants have been done after APAP overdose. The greatest challenge is early identification of patients destined for irreversible hepatic failure (see "Prognosis and Outcome" section of this chapter).

SPECIAL CONSIDERATIONS

Acute Overdose in Alcoholics and Other High-Risk Patients

Certain subgroups of patients appear to be at greater or lesser risk for APAP toxicity, but this fact is of more theoretic than practical value in the management of acute overdose. Higher risk is expected in patients with increased CYP2E1 enzyme activity from chronic use of agents that induce this enzyme (e.g., ethanol, barbiturates, phenytoin, sedative–hypnotics, griseofulvin, haloperidol, tolbutamide) [39] or decreased GSH stores or low GSH turnover rates (e.g., malnourished patients or those with liver disease). Lower toxicity might be expected when CYP2E1 activity is inhibited by chronic use of agents such as cimetidine or when a patient has coingested an agent that is metabolized by this enzyme, thus competing with APAP and decreasing NAPQI formation [2].

Acute overdose studies in animals demonstrated increased toxicity after chronic ethanol use and decreased toxicity when ethanol and APAP were coingested [40]. The protective effect of ethanol coingestion appears to be due to competitive inhibition of NAPQI formation by P450 ethanol metabolism. Chronic ethanol use, particularly in an alcoholic that is currently abstinent [41] could worsen toxicity by causing P450 induction, GSH depletion, or some other unknown mechanism. For example, an alcoholic might be protected by the acute coingestion of ethanol or be nutritionally deprived and have lower P450 activity.

Despite suggestions that some of these factors may be important [42], the amount of chronic ethanol or drug use that is clinically significant is unknown and certain to be variable.

Because the treatment nomogram line is conservative, treatment decisions after acute overdose should be made in the same manner as described previously, regardless of chronic coingestants.

Acute Overdose in Pediatric Patients

Of 417 children with acute APAP overdose, 49 of whom had plasma APAP levels over the nomogram line, indicating potential toxicity, only three (6.1%) developed an AST or ALT greater than 1,000 IU per L [43]. This incidence is less than that reported in adults, leading to speculation that children are relatively protected from APAP toxicity.

Several pharmacokinetic differences between children and adults have been noted. The most consistent finding is that the ratio of APAP-sulfate to APAP-glucuronide is higher in children than in adults [44], but this difference in nontoxic routes of metabolism has not been shown to be associated with a decrease in production of NAPQI. Thus, increased sulfation has not been proven favorably to alter NAPQI formation. Decreased P450 activity, and thus decreased NAPQI formation, has also been postulated in children, but decreased P450 activity is noted only in fetal and neonatal subjects [45]. Most APAP poisonings occur outside the newborn period, when P450 activity may be even greater than in adults. Hence, this theory cannot explain a hepatoprotective effect in older children. If children are actually less susceptible to APAP toxicity, it may be because of an increased ability to regenerate GSH, but this, too, is unproven.

Perhaps the most likely explanation is that pediatric overdoses are quantitatively less severe. In adults, particularly those treated late, the outcome is worse in patients with very high APAP levels [24]. Substantial toxicity has also developed in children with very high levels, but there are too few cases to

allow for any conclusions. Until larger numbers of children with very high APAP levels are studied, patients of all ages with a significant overdose must still be considered at substantial risk and managed accordingly. As with adults, the longer the time between ingestion and presentation or treatment in children with potentially toxic drug levels, the greater the incidence of hepatotoxicity and the worse the prognosis [21].

Acute Overdose in Pregnancy

Although experience with overdose in pregnancy is limited [46], certain conclusions seem valid. First, there is clear evidence that APAP overdose can result in morbidity and mortality to woman and fetus at all stages of pregnancy. Second, there currently is no evidence that NAC is harmful to a pregnant woman or her fetus. Third, NAC is hepatoprotective to the woman. Fourth, NAC crosses the human placenta [47], and this is likely to be beneficial to the fetus. On the basis of these observations, it is recommended that pregnant women be treated according to standard guidelines regardless of gestational age of the fetus and that newborns delivered during a course of maternal NAC treatment should also complete a course of NAC after delivery.

Acute Overdose of Extended-Release Acetaminophen

Because experience with ER APAP overdose is limited, the applicability of the nomogram, which was derived from clinical outcome data in patients with immediate-release APAP overdose, to those with ER APAP overdose remains to be determined [25–27]. Although it is agreed that patients who have a potentially toxic APAP level after acute acetaminophen ER overdose require NAC, the management of those with levels that are elevated but nontoxic is controversial. Some have suggested that such patients do not require NAC [48]. Given that peak drug levels after supratherapeutic but nontoxic doses of ER acetaminophen are only two-thirds of those seen after equivalent doses of an immediate-release formulation, despite nearly identical areas under the curve [49], others recommend treatment if any APAP level is two-thirds or more of the one that is indicated toxic by the nomogram [27].

Chronic Overdose

There are occasional reports of serious toxicity from chronic overdose in infants with acute febrile illness [19,21]. Chronic toxicity has also been reported after doses only slightly higher than recommended and even with therapeutic ones in adults with fasting and alcohol use [50]. Although alcoholics do appear to be at greater risk for toxicity from therapeutic doses, the validity of data on fasting has been questioned [51]. There is no evidence that this occurs in otherwise healthy individuals. Similarly, in the absence of continued ethanol abuse, there is no evidence that therapeutic dosing carries an increased risk in patients with cirrhosis or other forms of chronic liver disease [52]. On the basis of current knowledge, there is no reason to avoid APAP in any of these groups, although patients must be clearly instructed to avoid overdosing.

Evaluation of patients with chronic overdose should include a detailed history of the timing of doses, particularly the last dose; the amount ingested at each dose; possible increased risk factors (e.g., chronic alcoholism, use of other P450 inducers); symptomatology; an APAP level at least 4 hours after the last dose; and aminotransferase levels. In such cases, the nomogram has never been studied and has little or no validity. Because there are currently no reliable guidelines to assess risk, it is best then to consult with a toxicologist or regional poison center to determine the best course of action. One approach is to treat according to the guidelines discussed the next section.

Late Treatment

Treatment decisions in patients who present more than 24 hours after an overdose are problematic. Initial studies of the 20-hour intravenous NAC protocol suggested that NAC was of no value if started more than 12 to 15 hours after ingestion [28], and initial results of the 72-hour oral protocol indicated that treatment more than 16 hours after ingestion was ineffective [30]. As a result, studies of treatment initiated after 24 hours were not performed initially. More extensive data and analysis of patients treated with 72 hours of oral NAC revealed that patients first treated between 16 and 24 hours after overdose experienced less hepatotoxicity than untreated historical control subjects or historical control subjects treated late with a 20-hour course of intravenous NAC [24].

Subsequently, a series of studies showed theoretic and clinical benefit to late NAC administration [29,53,54]. In the most remarkable of these, NAC started a median of 53 hours after ingestion and after evidence of severe liver injury reduced morbidity and mortality [29]. Although the issue of which cases warrant late treatment is not well defined, the following approach to the treatment of patients who present late is offered: If the APAP level is undetectable and aminotransferase levels are normal, NAC is not indicated, because the possibility of hepatotoxicity is extremely low. If hepatotoxicity is evident, a full course of NAC is indicated. For patients who have detectable APAP levels and no hepatotoxicity, NAC therapy should be started. It can be discontinued before completing a full course of therapy when the APAP concentration falls to zero, as long as aminotransferase levels remain normal.

Short-Course ORAL Treatment

Treatment of acute APAP overdose with an abbreviated course of oral NAC is based on the observation that treatment for 20 hours with intravenous NAC [28] and for 48 hours with oral NAC [36] is just as effective as treatment with oral NAC for 72 hours [24] when treatment is started within 8 to 16 hours of ingestion (see previous section), and that patients who develop hepatotoxicity exhibit laboratory evidence of such toxicity within 24 to 36 hours of ingestion [9,55]. In short-course protocols, oral NAC is initiated in patients with toxic or potentially toxic APAP levels (by the nomogram) in the same dose as used in the standard 72-hour regimen, and APAP levels and aminotransferases are obtained at 24 and 36 hours postingestion. As with late treatment, if the APAP level becomes undetectable and aminotransferase levels are normal at either point in time, NAC is stopped, whereas if hepatotoxicity becomes evident, a full course of NAC is indicated. For patients who have detectable APAP levels and no hepatotoxicity, NAC therapy should be continued. It can be discontinued before completing a full course of therapy if the APAP concentration subsequently becomes undetectable and if aminotransferase levels remain normal. Although toxicologists have been successfully using short-course NAC therapy for years, published data are limited [56], and poison centers have been slow to adopt this approach. Hence, consultation with a toxicologist is advised when contemplating such treatment.

PROGNOSIS AND OUTCOME

Severe hepatotoxicity after APAP overdose has traditionally been defined by an ALT or AST greater than 1,000 IU per L, although most patients with such elevations have no significant short- or long-term sequelae. By using this definition, the risk of hepatotoxicity can be estimated based on the initial APAP concentration. Without NAC therapy, hepatotoxicity develops in less than 8% of all overdose patients, in 60% of probable risk cases (APAP concentration above a nomogram line intersecting 200 µg per mL at 4 hours and 50 µg per mL at 12 hours), and in 89% of high-risk cases (APAP concentration above a nomogram line intersecting 300 µg per mL at 4 hours and 75 µg per mL at 12 hours) [13].

Far less toxicity occurs in patients treated with NAC, although outcome depends on APAP concentration and the time NAC was started. Even in high-risk late-treated cases, only 41% of patients treated with oral NAC for 72 hours developed toxicity. Most important is that regardless of APAP level, NAC is extremely effective when started within 8 hours [24]. Hepatotoxicity occurred in less than 5% of patients in this subset.

Death is unusual after APAP overdose. When patients at probable risk for hepatotoxicity are considered, the reported mortality rate in untreated cases varies from 5.3% [28] to 24% [57]. A mortality rate of 1.1% has been noted in similar patients treated with the 20-hour intravenous NAC protocol [29], and it was found to be 0.68% in patients treated with the 72-hour oral NAC protocol [24]. In fact, even among high-risk cases first treated between 16 and 24 hours after overdose, the mortality rate was only 3.1% after oral NAC therapy [24].

It is not uncommon to see aminotransferase elevations greater than 10,000 IU per L during stage III, with eventual complete recovery [2]. As a result, aminotransferase levels alone are inadequate to judge prognosis. Evidence of hepatic dysfunction, such as marked elevations in prothrombin time and bilirubin, or evidence of persistent hypoglycemia, lactic acidosis, or hepatic encephalopathy, indicates true hepatic failure and a poor prognosis. Previous reports suggested that a bilirubin greater than 4 mg per dL or a prothrombin time greater than twice control indicates a poor prognosis [58]. More recently, a pH less than 7.30, prothrombin time greater than 100 seconds, serum creatinine greater than 3.4 mg per dL, and grade III or higher encephalopathy have been used to define poor prognosis [59], as has the single criterion of an increasing prothrombin time on day 4 after overdose [60] or a lactate of greater than 3.5 mmol per L shorter after admission [61]. Most recently, Schmidt and Dalhoff [62] demonstrated that an increasing alpha-fetoprotein serum concentration (particularly a concentration of more than 3.9 µg per L on the day after peak ALT) is associated with survival. As noted previously, patients meeting these criteria may benefit from NAC treatment [29,53]. Standard measures for the treatment of liver failure, including arrangements for possible liver transplantation, should also be provided.

The presence or absence of aminotransferase elevation at the time of treatment initiation appears to be the most sensitive early prognostic indicator. To date, all reported patients who died from APAP toxicity already had some degree of AST or ALT elevation at the time a 72-hour course of oral NAC was started [24]. Hence, all patients with liver enzyme values that are normal when oral NAC is started would be expected to survive.

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CHAPTER 119 ■ ALCOHOLS AND GLYCOL POISONING

JENNIFER L. ENGLUND, MARCO L.A. SIVILOTTI AND MARSHA D. FORD

The accidental or deliberate consumption of alcohols and glycols is a major cause of health problems [1,2]. Although light consumption of ethanol may be associated with health benefits in some populations [3–5], heavy consumption increases overall mortality, especially mortality due to trauma, suicide, cirrhosis, and malignancies [6]. Ethanol is estimated to contribute to 100,000 deaths annually in the United States; with economic costs in excess of $200 billion [7,8]. Ethanol is involved in at least 10% of fatalities reported to US poison centers, and other alcohols and glycols, especially methanol and ethylene glycol, are responsible for another 3% of all fatalities [9]. These so-called toxic alcohols, namely methanol and ethylene glycol, are usually involved in sporadic poisonings, often involving the accidental exposure of a young child to automotive or household products or the intentional suicidal ingestion in adults. Furthermore, multiple-victim poisonings can occur after recreational substitution for ethanol, during illicit manufacture of ethanol, or after the addition of other glycol products [10–12].

ETHANOL

Ethanol is consumed by most adults and is the most serious drug of abuse in Western society. Approximately one-third of the US population can be categorized as moderate-to-heavy drinkers, consuming four or more alcoholic drinks per week and of these, about one in five can be considered problem drinkers or alcoholics [13]. Ethanol use is a factor in about 8% of emergency department visits [14], 10% to 50% of hospital admissions [15], and its projected economic costs due to job absenteeism and poor job performance are staggering [8,13]. Chronic ethanol consumption can cause multiorgan system

TABLE 119.1

COMPARATIVE DATA ON THE TOXIC ALCOHOLS AND GLYCOLS

Substance	Formula	Molecular weight	Specific gravity	V_d (L/kg)	Elimination half-life ($t^{1}/_{2}$)	Boiling point (°C)	Onset of toxicity	Important metabolites
Ethanol	$CH_3\,CH_2OH$	46	0.79	0.6	Zero order at 15–30 mg/dL/h	78.5	30–60 min	Acetaldehyde Acetic acid
Methanol	CH_3OH	32	0.79	0.7	Zero order at 8.5 mg/dL/h without ethanol; first order: $t^{1}/_{2}$ = 46.5 h with ethanol or fomepizole and 2.5 h with hemodialysis	64.7	12–24 h[a]	Formaldehyde Formic acid
Ethylene glycol	$CH_2(OH)–CH_2(OH)$	62	1.11	0.68	First order: $t^{1}/_{2}$ = 2.5–4.5 h without ethanol and with normal kidneys, 17 h with ethanol or fomepizole and < 3 h with hemodialysis	197.6	4–12 h[a]	Glycoaldehyde Glyoxylic acid Glycolic acid Oxalic acid
Isopropanol	$CH_3\,CH(OH)CH_3$	60	0.79	0.6–0.7	First order: $t^{1}/_{2}$ = 2.5–3.5 h	82.5	30–60 min	Acetone
Propylene glycol	$CH_2(OH)\,CH(OH)CH_3$	76	1.04	0.55	First order: $t^{1}/_{2}$ = 2–5 h in adults, 19.3 h in infants	188.2	Seconds with intravenous, ? with dermal	Pyruvate Lactate Acetate
Benzyl alcohol	$C_6H_5–CH_2OH$	108	1.04	?	?	204.7	?	Benzoic acid Hippuric acid
Diethylene glycol	$CH_2(OH)\,CH_2\,O\,CH_2\,CH_2(OH)$	106	1.12	?	?	245	?	2-Hydroxyethoxyacetic acid

[a]For metabolite effects; may be longer if ethanol coingested.
V_d, volume of distribution.
Data from Refs. [74,80,81,86,91,92,94,103–105,109,127,128,130,146].

disease, nutritional disorders, and teratogenic effects. In addition to beverages (typically 4% to 50% ethanol by volume), ethanol can be found in a myriad of colognes, perfumes, mouthwashes, aftershaves, and over-the-counter medicinals. Many of these products contain 50% to 99% ethanol and can be sources for intoxication, especially for children [16].

The chemical properties and kinetics of ethanol are summarized in Table 119.1. Ethanol is a small, slightly polar aliphatic alcohol with a weak electric charge, miscible in water and lipids. It diffuses easily into all body tissues. It is postulated that ethanol influences multiple ion channels, possibly by causing subtle alterations in their tertiary structure or their dynamic interaction with cell membranes. The behavioral effects of ethanol may result from its ability to antagonize the excitatory *N*-methyl-d-aspartate–glutamate receptor and to potentiate the inhibitory γ-aminobutyric acid A receptor [17–20]. Ethanol is also known to interact with glycine, nicotinic acetylcholine, 5-HT_3, and P_{2X} purinergic receptors, as well as the L-type calcium- and potassium-channel proteins [21,22]. The major metabolite, acetate, has been shown to mimic adenosine's effects via the P_1 receptor [23]. The precise role of these and other effects in producing intoxication, dependence, and withdrawal (see Chapter 145) is uncertain.

Ethanol is readily absorbed from the gastrointestinal tract, with 57% of the absorption occurring in the small intestine. Peak ethanol levels typically occur 30 to 60 minutes after ingestion if the stomach is empty [16]. Women have higher peak ethanol concentrations after a given dose because of smaller body mass and smaller relative body water, rather than gender differences in gastric mucosal alcohol dehydrogenase (ADH) activity [24–27].

Metabolism of ethanol occurs predominantly in the liver by three enzymatic systems: the cytosolic ADH enzyme family (especially class I), the cytochrome P450 enzymes (microsomal ethanol oxidizing system, largely CYP2E1 but also 3A4 and 1A2), and peroxisomal catalase [28]. Metabolism is Michaelis–Menten with zero-order kinetics prevailing at levels over 100 mg per dL [29]. Only a small fraction of ethanol is exhaled or secreted in urine and sweat [13,30].

ADH is responsible for greater than 57% of ethanol metabolism at low doses. In the ADH metabolic pathway (Fig. 119.1), ethanol is oxidized to acetaldehyde and then to acetate in a process that reduces oxidized nicotinamide adenine dinucleotide (NAD^+) to nicotinamide adenine dinucleotide (NADH). The increased ratio of NADH to NAD^+ can inhibit NAD^+-dependent reactions, such as gluconeogenesis,

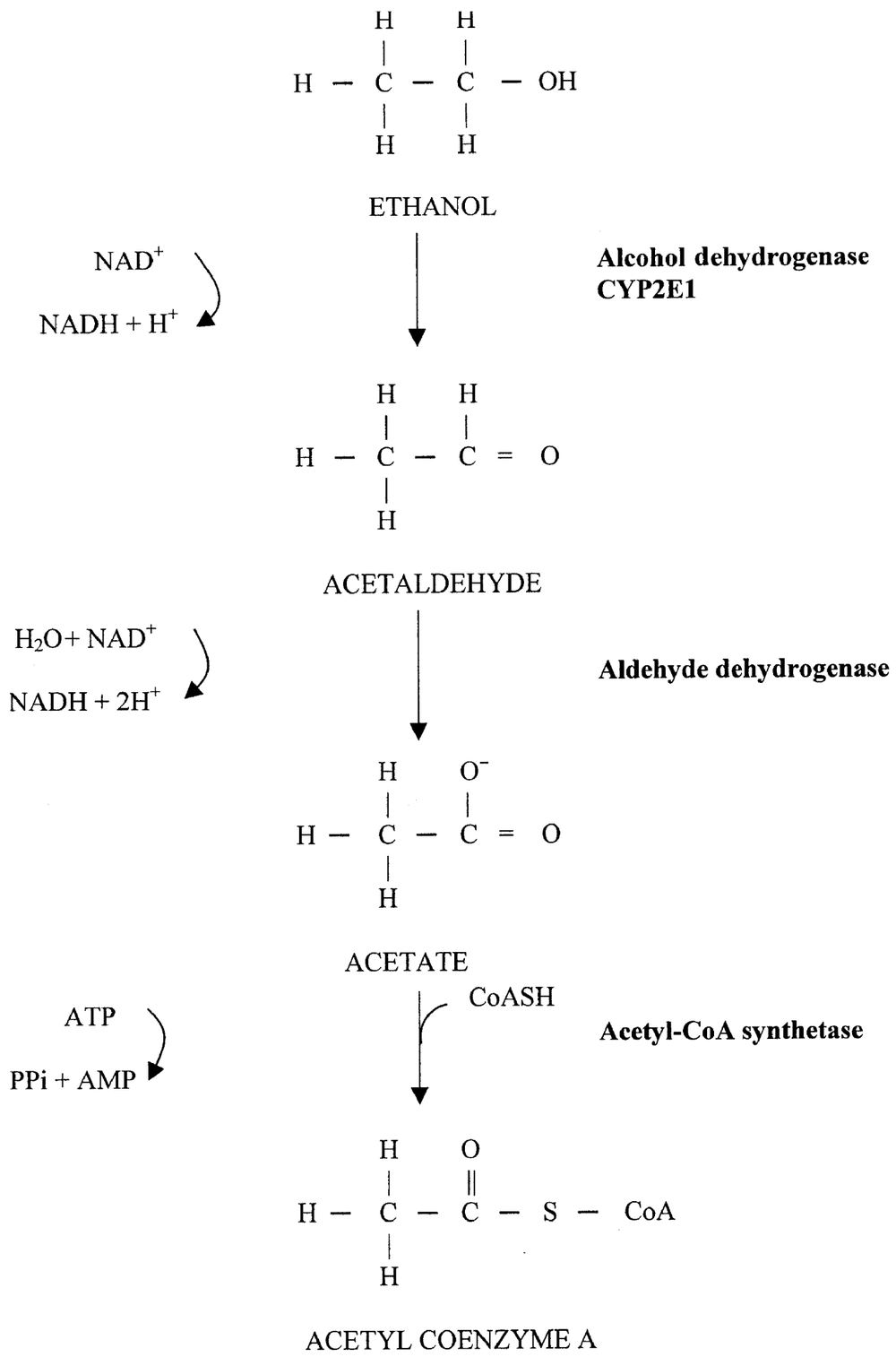

FIGURE 119.1. Ethanol metabolism. AMP, adenosine monophosphate; ATP, adenosine triphosphate; Co, coenzyme; NAD^+, oxidized form of nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; PPi, inorganic pyrophosphate.

as well as slowing subsequent ethanol oxidation and clearance [31]. Acetate is linked to coenzyme A (acetyl-CoA), which can then participate in the citric acid cycle, fatty acid synthesis, or ketone formation [30]. Genetic variations in ADH and aldehyde dehydrogenase have been extensively characterized and may play a role in determining susceptibility to alcoholism [32–35]. Normally, the cytochrome P450 and catalase systems play minor roles in ethanol metabolism [36,37]. Chronic ethanol use can induce CYP2E1 activity 4- to 10-fold, allowing habitual users to metabolize ethanol twice as quickly as occasional drinkers [38].

Ethanol is a central nervous system (CNS) depressant. After acute ingestion, there is often an initial stage of paradoxical excitation due to release of learned social inhibitions. For nontolerant individuals, a blood ethanol concentration as low as 20 mg per dL impairs driving-related skills involving perception and attention [39]. At concentrations of 50 mg per dL, gross motor control and orientation may be affected, and intoxication may become apparent [40]. Lethargy, ataxia, and muscular incoordination may be seen at serum levels of 150 mg per dL or greater, coma at approximately 250 mg per dL, and death with levels greater than 450 mg per dL [16,41]. Tolerant drinkers can achieve higher levels before developing similar symptoms, and survival has been reported despite a serum level of 1,500 mg per dL [42]. At high doses, ethanol functions as an anesthetic, causing CNS depression, autonomic dysfunction (e.g., hypotension, hypothermia), coma, and death from respiratory depression and cardiovascular collapse. The estimated LD_{50} in adults is 5 to 8 g per kg and 3 g per kg for children [16].

Tolerance to ethanol's effects develops both acutely and after chronic consumption. With acute consumption, the physiologic effects at a given serum level of ethanol have been noted to be less when ethanol concentrations are declining rather than when levels are rising (Mellanby effect) [43]. Compared with inexperienced drinkers, chronic drinkers experience diminished effects to a given amount of ethanol. Tolerance is accompanied by changes in membrane-associated receptors [21,22].

Clinical Manifestations

Patients may present with varying degrees of altered consciousness, including agitation, stupor, and coma. The odor of ethanol or its congeners on their breath is usually present. Slurred speech, ataxia, and nystagmus are noted in patients with mild to moderate intoxication. Disconjugate gaze is frequently seen in comatose patients. Acute intoxication may be accompanied by vomiting, particularly in novice drinkers. Children younger than 10 years of age are most susceptible to alcohol-induced hypoglycemia, which can occur at relatively low serum ethanol levels (discussed later).

Diagnostic Evaluation

The physical examination should be directed toward evaluation of the airway and a search for complicating or contributing factors such as trauma, infection, and hemorrhage. In patients with moderate-to-severe poisoning, laboratory studies including complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine, glucose, ethanol, magnesium, calcium, and phosphorus level, liver function tests, prothrombin time, electrocardiogram, chest radiograph, arterial or venous blood gas, and urinalysis should be obtained as clinically indicated. If the level of consciousness is inconsistent with the serum ethanol level or does not improve over a few hours, the physician should reconsider the diagnosis of ethanol intoxication (Table 119.2).

Management

Patients with stupor or coma who cannot be aroused to a verbal (but not necessarily coherent) state or who have a poor respiratory effort should be intubated to ensure airway patency and to protect against pulmonary aspiration. Intravenous (IV) naloxone (0.1 to 2 mg), dextrose (25 to 50 g) and thiamine hydrochloride (100 mg) should be administered when opioid toxicity, hypoglycemia, or Wernicke's encephalopathy are considerations.

Activated charcoal should be withheld unless potentially toxic coingestants are suspected. Hypothermia, if present, is usually mild in the absence of environmental exposure, and can be managed with warm blankets. Nutritional, electrolyte, and fluid deficiencies should be corrected. A variety of interventions trying to increase ethanol clearance or decrease its effects, including supplemental IV fluids, dextrose, and fructose, are neither clinically useful nor recommended [44,45].

ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis (AKA) develops as a result of hormonal, nutritional, and metabolic changes caused by ethanol (Fig. 119.2). Because ethanol retards ketogenesis, AKA usually occurs when ethanol levels are low to absent [30]. Ethanol

TABLE 119.2

DIFFERENTIAL DIAGNOSES FOR ACUTE ETHANOL INTOXICATION

Metabolic
Hypoglycemia
Hyperglycemia
Hyponatremia
Hypothermia
Hepatic encephalopathy
Disulfiram reaction
Hypercalcemia
Hypoxia
Drug intoxication
Phencyclidine
Opioids
Cyclic antidepressants
Other alcohols (methanol, isopropanol, ethylene glycol)
Other sedative-hypnotics (meprobamate, methaqualone, glutethimide, benzodiazepines, barbiturates, chloral hydrate, ethchlorvynol, methyprylon)
Anticholinergics
Carbon monoxide
Trauma
Intracranial hemorrhage (subdural, epidural, intracerebral bleed)
Infections
Central nervous system infections
Acquired immunodeficiency syndrome
Sepsis
Neurologic
Postictal
Delirium tremens
Wernicke's encephalopathy

Adapted from Adinoff B, Bone GHA, Linnoila M: Acute ethanol poisoning and the ethanol withdrawal syndrome. *Med Toxicol* 3:172, 1988.

metabolism indirectly impairs gluconeogenesis and increases fatty acid and ketone formation. Inadequate nutritional intake in alcoholics depletes glycogen, minerals, and vitamin stores. Vomiting results in decreased intravascular volume and increased catecholamine levels that blunt insulin release [46] activate lipase, and accelerate free fatty acid oxidation. Glucagon activates the carnitine acyltransferase system producing excess acetyl-CoA.

Acetyl-CoA cannot be used by mammals to form pyruvate or higher carbohydrates. Instead, it can undergo only three metabolic fates: fatty acid synthesis, oxidation to CO_2 in the citric acid cycle, and cholesterol or ketone body formation via 3-hydroxy-3-methylglutaryl-CoA. The ketogenic pathway has the largest capacity and requires the least adenosine triphosphate for handling acetyl-CoA overload [46]. Nutritional deficiencies impair acetyl-CoA conversion to triglycerides and its entrance into the citric acid cycle [30]. Finally, the increased NADH to NAD^+ redox ratio caused by ethanol oxidation favors the conversion of acetoacetate to β-hydroxybutyrate, which is largely responsible for the ketoacidosis.

Other acid–base abnormalities may occur in alcoholics. Respiratory acidosis may be caused by hypoglycemia or ethanol-induced respiratory depression. Lactic acidosis can occur secondary to seizure activity, an increase in the NADH to NAD^+ ratio that favors lactate formation from pyruvate, decreased gluconeogenesis, thiamine deficiency impairing pyruvate's entry into the citric acid cycle, and liver dysfunction [47]. Vomiting may cause volume contraction, hypokalemia, and metabolic alkalosis [46]. A mild acetic acidosis may be seen when peripheral tissues incompletely oxidize acetate. An unexplained hyperchloremic metabolic acidosis has been observed in acutely intoxicated patients [47].

Clinical Manifestations

Patients with AKA usually present with a recent history of binge alcohol drinking and poor nutritional intake followed by vomiting. The fruity odor of ketones may be detected along with Kussmaul's breathing, dry mucous membranes, tachycardia, orthostatic hypotension, and poor skin turgor [30].

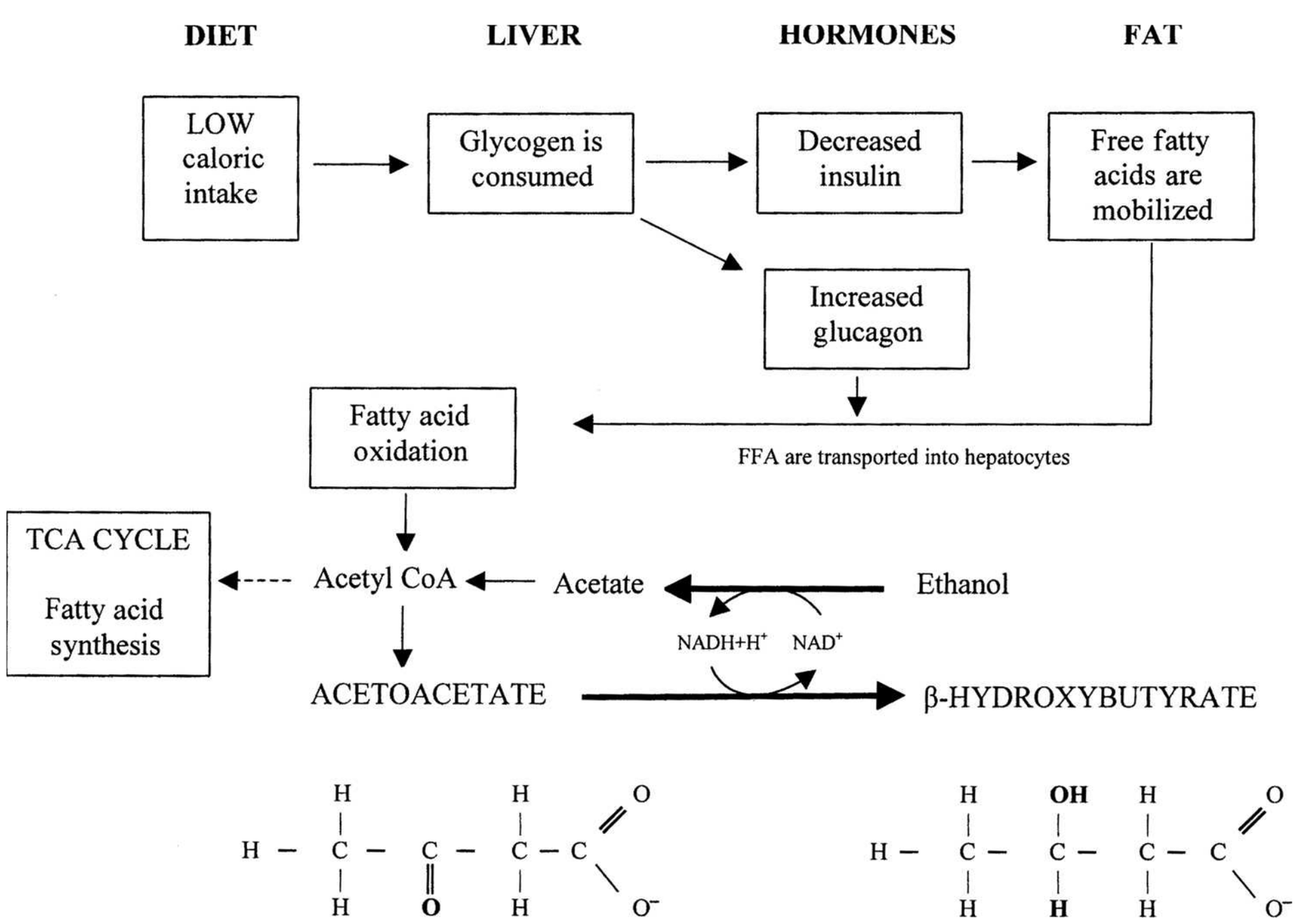

FIGURE 119.2. Mechanism of alcoholic ketoacidosis. Co, coenzyme; FFA, free fatty acids; NAD^+, oxidized form of nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; TCA, tricarboxylic acid cycle (also known as *citric acid cycle*). [Adapted from Eckardt MJ, Harford TC, Kaelber CT, et al: Health hazards associated with alcohol consumption. *JAMA* 246:648, 1981, with permission.]

Abdominal pain is typical, with nonspecific tenderness on examination [48].

Diagnostic Evaluation

The diagnosis of AKA is a diagnosis of exclusion. Signs and symptoms of concomitant gastritis, pancreatitis, hepatitis, gastrointestinal hemorrhage, and vitamin and mineral deficiencies are often present. Laboratory studies should include those listed for acute ethanol intoxication plus serum ketones, lactate, and osmolality. Ethanol levels are often low to undetectable, and hypoglycemia may be present [49,50]. A respiratory or metabolic alkalosis may be present in addition to the anion gap metabolic acidosis. At presentation, the predominant serum ketone is usually β-hydroxybutyrate due to the altered redox state, which results in falsely low serum ketones by the semi-quantitative nitroprusside test for acetoacetate [30]. Many laboratories now measure β-hydroxybutyrate directly to mitigate this concern. Hypokalemia is uncommon, in part because acidosis shifts potassium out of the cell. The osmol gap may be elevated from glycerol, acetone, and its metabolites [51], even after correcting for the serum ethanol concentration [52].

The differential diagnosis of an anion gap metabolic acidosis includes lactic acidosis; salicylate poisoning; uremia; diabetic ketoacidosis; and intoxication from iron, ibuprofen, toluene, methanol, ethylene glycol, and diethylene glycol. Hypoxia and hypotension are the most common causes of lactic acidosis, but malignancies, leukemia, and toxicity due to cyanide, metformin, and carbon monoxide should also be considered [53]. AKA can usually be differentiated from diabetic ketoacidosis by the lack of significant hyperglycemia, minimal alteration of consciousness, a relatively mild acidosis, and rapid improvement with supportive therapy [54]. The presence of more than mild tenderness on abdominal examination should prompt investigation for other pathology such as pancreatitis, hepatitis, sepsis, or pneumonia [48].

Management

Supportive therapy is the same as that noted for acute intoxication. IV fluid resuscitation, glucose (25 to 50 g), and thiamine (100 mg) reverse the ketogenic process and are the mainstays of therapy. Maintenance fluids should consist of dextrose (5%) in normal saline [30]. Thiamine facilitates the entry of pyruvate into the citric acid cycle and protects against Wernicke's encephalopathy [55]. Once urine output is established, supplemental potassium and magnesium should be administered. Hypophosphatemia may develop with increased glycolysis and carbohydrate refeeding and should be corrected with potassium phosphate [49,54]. Hospitalization and refeeding of malnourished patients may be required.

ETHANOL-RELATED HYPOGLYCEMIA

Four types of hypoglycemia associated with or induced by ethanol have been delineated: alcohol-induced fasting hypoglycemia, reactive hypoglycemia of chronic alcoholism, alcohol potentiation of drug- or exercise-induced hypoglycemia, and alcohol-promoted reactive hypoglycemia [56]. Alcohol-induced fasting hypoglycemia is the best understood. Marginal nutritional status is the only requirement for its development, and it can occur in poorly nourished alcoholics and in young children, fasted normal subjects, patients on low-carbohydrate diets, and those with thyrotoxicosis and adrenocortical deficiency [49,56,57]. When these patients consume ethanol rather than food, their marginal glycogen stores are readily depleted by glycogenolysis and the body's metabolic needs become dependent on gluconeogenesis. Ethanol inhibits this reaction [57], however, probably by the increasing NADH to NAD^+ ratio. This effect preferentially shunts pyruvate to lactate and thus blocks pyruvate from participating in gluconeogenesis or other reactions in which it is the key intermediate (Fig. 119.3) [30].

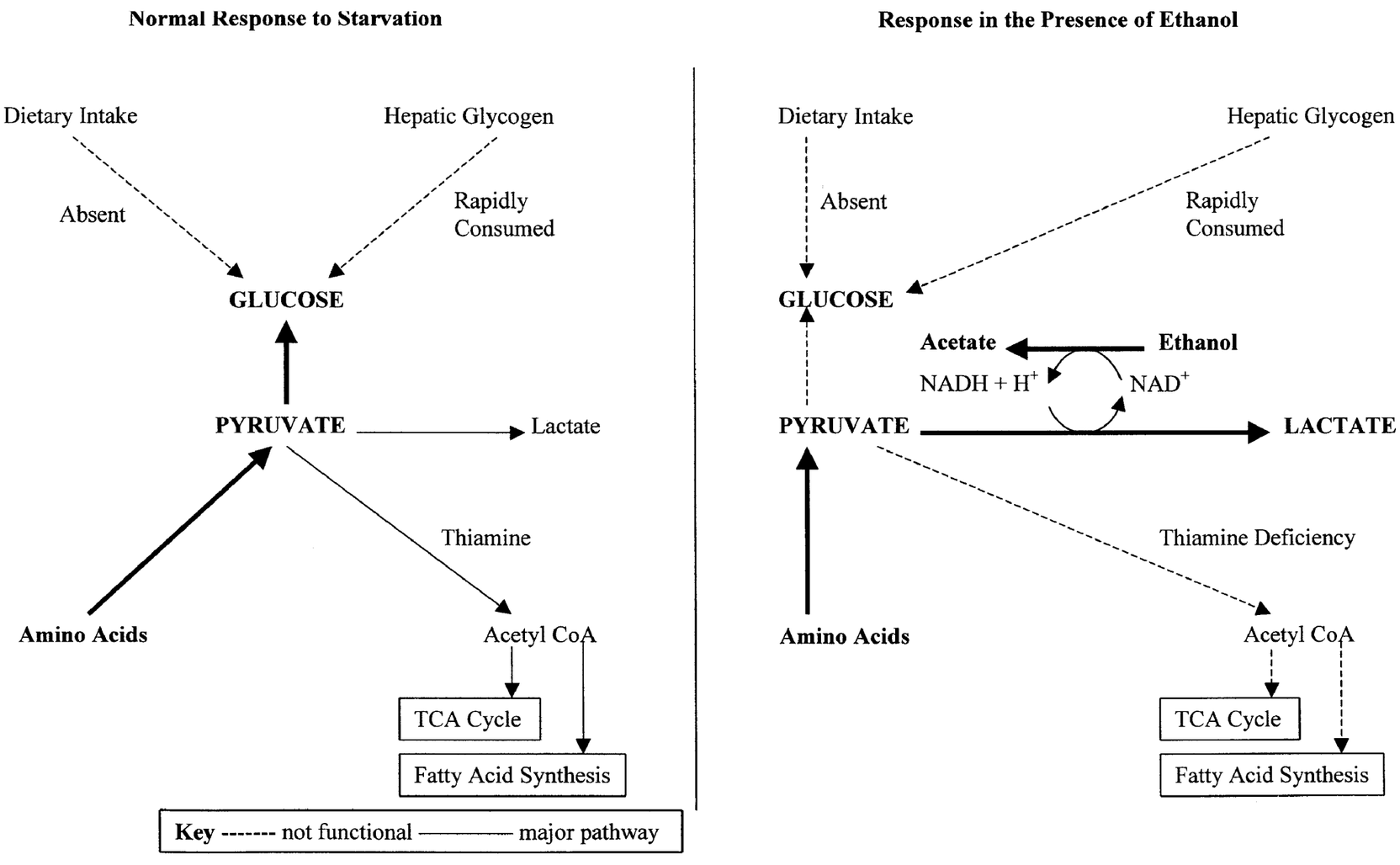

FIGURE 119.3. Ethanol-induced hypoglycemia. Co, coenzyme; NAD^+, oxidized form of nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide; TCA, tricarboxylic acid cycle (also known as *citric acid cycle*). [Adapted from Hoffman RS, Goldfrank LR: Ethanol-associated metabolic disorders. *Emerg Med Clin North Am* 7:943, 1989, with permission.]

Contributory endocrinologic abnormalities may include impaired cortisol release and decreased growth hormone secretion due to hypothalamic–pituitary dysfunction [56,57]. Lactic acidosis may result from excessive lactate production [57].

The biochemical mechanisms underlying the other types of hypoglycemia are poorly understood [56,58], but alcohol-promoted reactive hypoglycemia may be due to potentiation of insulin secretion by ethanol [56]. Liver disease is not necessary for the development of hypoglycemia [59].

Clinical Manifestations

CNS depression ranging from confusion to coma, seizures, and symptoms of increased sympathetic activity such as diaphoresis, anxiety, tremulousness, palpitations, and weakness are the hallmarks of hypoglycemia. Hypothermia occurs frequently [56].

The CNS effects of hypoglycemia and ethanol intoxication can mimic one another, whereas hypoglycemia-induced adrenergic signs and symptoms can be mistaken for ethanol withdrawal. The differential diagnoses are similar to those for acute ethanol intoxication (Table 119.2).

Diagnostic Evaluation

Laboratory evaluation is the same as for a patient with acute intoxication. If metabolic acidosis is present, the studies recommended for AKA are also indicated. Serum glucose concentrations are usually less than 40 mg per dL, ethanol levels are often low [56], and lactate levels may be elevated [57].

Caution is advised when assessing capillary blood glucose levels with point-of-care testing. Errors can be introduced by the age of the strips, and by the accuracy of machines used to read them especially outside the calibration range. The effect of varying ethanol levels on the accuracy of these strips has not been adequately studied. Given the morbidity and mortality of severe hypoglycemia, the potential errors in testing, and the benign nature of IV glucose, all symptomatic patients with an equivocal glucose reading should be treated with glucose, especially if diabetic or alcohol impaired [30].

Management

Therapy for ethanol-induced hypoglycemia parallels that for acute ethanol intoxication. An IV dextrose bolus of 25 to 50 g should be followed by a 10% dextrose infusion. In young children, 25% dextrose should be given in a bolus of 0.25 to 1 g per kg, followed by a maintenance infusion. Blood glucose levels should be frequently monitored and repeat dextrose boluses may be necessary.

Most patients immediately respond to therapy and return to normal levels of consciousness without major morbidity, but persistent encephalopathy and death have been reported [30].

ETHYLENE GLYCOL AND METHANOL

Ethylene Glycol

Ethylene glycol (1,2-ethanediol) is a colorless, sweet liquid [60,61] that imparts a warm sensation to the tongue and esophagus when swallowed. It is found primarily in automotive antifreeze solutions. Ingestions usually result from suicide attempts, intentional substitution of ethylene glycol for ethanol,

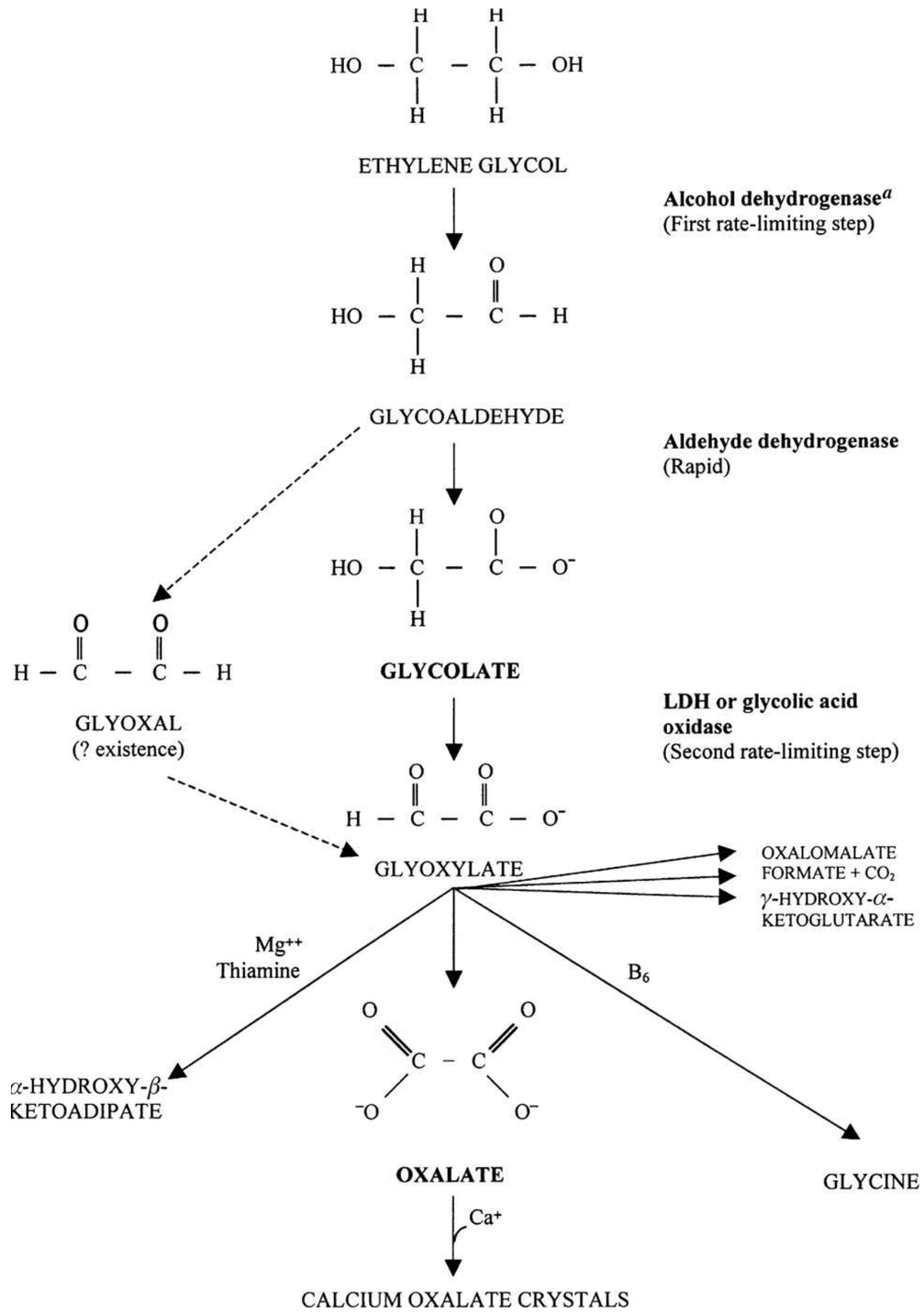

FIGURE 119.4. Ethylene glycol metabolism. [a]Blocked by ethanol and fomepizole. LDH, lactate dehydrogenase.

or accidental exposure. Ethylene glycol itself causes little toxicity other than ethanol-like inebriation until it is metabolized in the liver into its toxic acid metabolites (Fig. 119.4). Ethylene glycol is first metabolized in the liver by ADH to glycoaldehyde, which is rapidly transformed via aldehyde dehydrogenase to glycolic acid. Glycolic acid is slowly converted to glyoxylic acid, which in turn is converted to multiple metabolites, including oxalic acid [61,62]. It is uncertain which of these metabolites is most directly responsible for renal tubular toxicity [63–65].

The anion gap metabolic acidosis seen in ethylene glycol poisoning is due predominantly to elevated glycolic acid levels, [62,66–68] although oxalic acid, glyoxylic acid and glycoaldehyde may be more toxic [61,62]. Elevated lactic acid levels contribute to the acidosis [62,67–72], and have been attributed to the increased NADH to NAD^+ ratio caused by metabolism of ethylene glycol [64,73], and to the toxicity of glyoxylic acid on mitochondrial respiration [61,62,74]. Some lactate assays may misinterpret glycolate as lactate and report falsely elevated lactate levels [75–77].

Pathologic changes are noted in the CNS, kidneys, lungs, heart, liver, muscles, and retina [16,78]. Renal findings include dilation of the proximal tubules with swelling and vacuolization of the epithelial cells, distal tubular dilation, intratubular deposition of calcium oxalate crystals, and interstitial edema [73]. Pulmonary edema, interstitial pneumonitis, and hemorrhagic bronchopneumonia may occur. In some cases, interstitial myocarditis, skeletal muscle inflammation, and centrilobular hepatic fatty infiltration may develop. CNS findings include cerebral edema, meningoencephalitis, and cerebellar changes, including focal loss of Purkinje cells [78].

The chemical properties and kinetics of ethylene glycol are summarized in Table 119.1. Oral absorption of ethylene glycol occurs rapidly. Percutaneous absorption through intact skin is negligible. Ethylene glycol has a high boiling point and toxicity from vapor inhalation does not occur. Hepatic metabolism predominates yet renal elimination of the parent compound is initially substantial. The ensuing renal failure markedly prolongs the elimination of ethylene glycol and its metabolites [67,73,79,80].

The reported minimum lethal dose is 1.6 g per kg in humans. Hence, the estimated fatal dose widely quoted for a 70-kg person is 100 mL of 100% ethylene glycol, but this value is based on limited data [81] and assumes no treatment. With early and intensive treatment, survival has been reported in patients with serum ethylene glycol concentrations as high as 1,889 mg per dL [70,82,83].

Methanol

Methanol is a colorless liquid and has an odor distinct from that of ethanol [84,85]. Dietary sources and endogenous metabolism can produce serum methanol levels of 0.15 mg per dL [86]. Exogenous sources of methanol include windshield washing fluid, de-icing fluids, carburetor cleaners, paint removers, and paint thinners.

Methanol is oxidized in the liver by ADH to formaldehyde, which is quickly converted to formic acid (formate) by hepatic aldehyde dehydrogenase (Fig. 119.5). In primates, formate accumulates due to saturation of one-carbon metabolism. High levels of formate, an inhibitor of mitochondrial cytochrome oxidase, cause histotoxic hypoxia and are responsible for the characteristic metabolic acidosis and ocular toxicity seen with methanol toxicity [73]. Formaldehyde is also very toxic, but it has a very short half-life.

Formate plays a pivotal role in methanol toxicity. Blood formate concentrations account for nearly the entire observed anion gap and base deficit [87–89]. Symptoms and prognosis also correlate better with formate than with methanol levels [90,91]. Primates infused with formic acid develop ocular toxicity, even when the acidosis is controlled with sodium bicarbonate [92]. Ocular toxicity results from the inhibition of cytochrome oxidase by formic acid in the optic nerve, leading to disruption of mitochondrial electron transport and decreased axoplasmic flow and electrical conduction [93]. Although this produces changes in the optic nerve head, direct retinal toxicity can also occur [94].

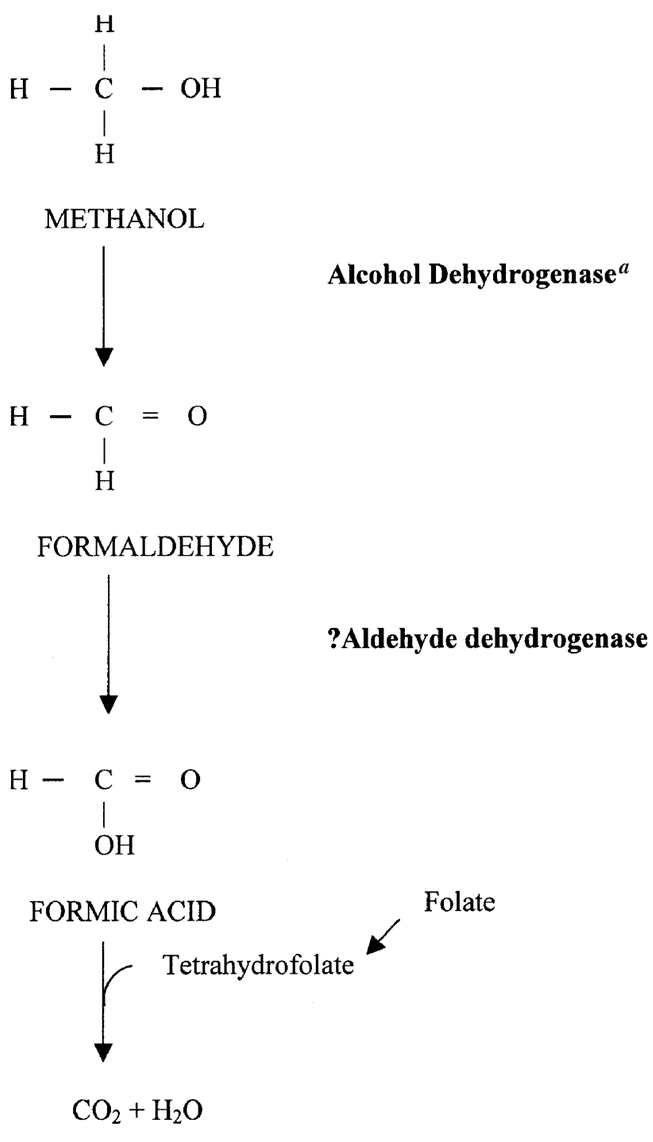

FIGURE 119.5. Methanol metabolism. [a]Blocked by ethanol and fomepizole.

The chemical properties and kinetics of methanol are summarized in Table 119.1. Methanol is absorbed orally, dermally, and via inhalation [84,95]. Exposure can occur intentionally or accidentally, as occurred in Estonia in 2001 when 68 patients died after consuming illegal spirits contaminated with methanol [96]. A retrospective hospital record review of 16 individuals who inhaled carburetor cleaning fluid fumes identified 48 hospital presentations with serum methanol levels greater than 20 mg per dL and 19 greater than 50 mg per dL [74]. Methanol's metabolism is slower than that of ethylene glycol or ethanol [73], which may explain why methanol toxicity develops more slowly. Hepatic oxidation predominates, with only trivial amounts eliminated via the lungs and kidneys [84]. Elimination follows first-order kinetics at low doses and during hemodialysis [97–99]. At higher doses, zero-order (Michaelis–Menten) kinetics may prevail. In one untreated patient, methanol elimination occurred at a rate of 8.5 mg per dL per hour [100]. The elimination half-life of formate in one untreated patient was 3.7 hours [90], and averaged 3.4 ± 1.5 hours in eight patients treated with fomepizole (4-methylpyrazole) and leucovorin [89]. With hemodialysis, the formate elimination half-life was estimated to be between 1.1 and 2.8 hours [87,89,90].

Reported lethal doses in patients with inadequate, delayed, or no therapy vary considerably and are not well established. In one epidemic, the minimal lethal dose was 15 mL of a 40%-by-weight methanol solution. In another outbreak, one patient survived a 600-mL ingestion of pure methanol but had permanent sequelae, whereas another reportedly imbibed 500 mL without complications [10].

Clinical Manifestations

Ethylene Glycol

Ethanol-like intoxication usually begins within an hour of ingestion. Symptoms due to toxic metabolites usually occur 4 to 12 hours after ingestion, but are delayed further if ethanol was coingested by delaying the metabolism of ethylene glycol. Patients may present alert, intoxicated, or in a coma, depending on the time since ingestion, the dose of ethylene glycol, coingestion of ethanol, and cross-tolerance [61,62,73,78,101,102]. Vital signs can be normal. Ocular exposure can produce a chemical conjunctivitis and chemosis [78], but systemic toxicity does not occur.

The classic division of ethylene glycol poisoning into three stages is primarily of historical interest. In reality, patients rarely exhibit sequential toxicity that can be readily divided into distinct stages. Shortly after ingestion and before significant metabolism of ethylene glycol has occurred, CNS effects such as ethanol-like intoxication, stupor, nausea, and vomiting predominate. As toxic metabolites begin to accumulate, a metabolic acidosis ensues with associated cardiovascular and pulmonary signs, including Kussmaul's respirations, tachycardia, cyanosis, and cardiogenic or noncardiogenic pulmonary edema [101]. As renal injury progresses, flank pain and tenderness, proteinuria, and anuria may occur. Acute renal failure occurs in nearly all untreated patients who manifest

metabolic acidosis (serum bicarbonate less than 10 mmol per L). Renal dysfunction can develop within 9 hours of ingestion [103]. Patients may also develop myositis with muscle tenderness and elevated creatine kinase [61,73]. Death may result from severe metabolic derangements, cardiovascular or respiratory failure, or progressive CNS depression. Prolonged seizures, coma, and a cerebral herniation syndrome have also been reported [104]. Preterminal dysrhythmias and hypotension are rare [70]. The presence of hyperkalemia, severe acidemia, seizures, and coma at presentation demonstrate severe toxicity.

Seizures are usually generalized but do not occur in all cases. Jacksonian seizures have been reported, as have myoclonic jerks and tetanic contractions due to hypocalcemia [70,78]. Progressive CNS depression and prolonged seizures usually result from cerebral edema [73]. Transient nystagmus and cranial nerve (II, V, VI, VII, VIII, IX, and X) palsies have been reported to occur 4 to 18 days postingestion [82,104–107].

Methanol

Onset of toxicity usually occurs within 30 hours of methanol ingestion [108]. In one epidemic, a range of 40 minutes to 72 hours was reported. Factors influencing time to symptoms include the dose, ethanol coingestion, and folate stores [85,108].

Neurologic, ophthalmologic, and gastrointestinal symptoms predominate [20,21,97,98,109,110]. Methanol is a less potent CNS depressant than ethanol. Patients may be alert on admission and complain only of headache and dizziness. Amnesia, restlessness, acute mania, lethargy, confusion, coma, and convulsions may follow. Cases mimicking subarachnoid hemorrhage with severe headache, vomiting, hypertension, and bradycardia followed by loss of consciousness have been described. Dyspnea is reported by only 8% to 25% of patients [96].

Early on, many patients offer no visual complaints. Visual symptoms accompany the metabolic acidosis and usually develop when the blood pH falls below 7.2. Blurred vision, photophobia, scotomata, eye pain, partial or complete loss of vision, and visual hallucinations (e.g., bright lights, "skin over eyes," "snowstorm," dancing spots, flashes) have been reported. These disturbances can persist after formate has been completely eliminated and the acidosis has resolved.

Methanol can produce severe hemorrhagic gastritis and pancreatitis, causing upper abdominal pain, nausea, vomiting, and diarrhea. Liver function abnormalities have been documented in moderately to severely ill patients.

Vital signs may reveal tachycardia and Kussmaul's respirations, but the blood pressure is usually maintained. Untreated, patients can die from sudden respiratory arrest [84]. The skin may be cool and diaphoretic, and abdominal muscles rigid without rebound tenderness.

The most notable physical findings are those discovered on ophthalmologic examination, but these are late findings. Pupils may react sluggishly or may be fixed and dilated [10]. Funduscopic examination may show hyperemia of the optic discs followed by retinal edema, which develops initially along the retinal vessels and then spreads to the central areas of the fundus. Retinal vessel engorgement accompanies the retinal edema [110]. Papilledema may develop [20]. Ophthalmologic findings do not necessarily correlate with visual complaints.

Diagnostic Evaluation

Poisoning by ethylene glycol and methanol should be suspected in all patients with a history of ingesting ethanol substitutes or who have an unexplained anion gap metabolic acidosis.

Ethylene Glycol

Laboratory studies should include complete blood cell count; serum electrolytes; glucose; blood urea nitrogen; creatinine; arterial or venous blood gas; calcium; serum osmolality; ethanol, methanol, and ethylene glycol levels; and urinalysis. Additional laboratory studies may include electrocardiogram, chest radiograph, and head computed tomography as clinically indicated. Early after ingestion, before significant metabolism of ethylene glycol, an osmol gap may be present [111] with neither metabolic acidosis nor an anion gap (see later discussion on osmol gap). As ethylene glycol is metabolized, the osmol gap decreases and an anion gap metabolic acidosis develops. Patients who present very late may have renal failure with normal osmol and anion gaps, normal pH, and unmeasurable ethylene glycol levels.

Perhaps the greatest diagnostic challenge in managing a patient suspected to have ingested a toxic alcohol or glycol is the limited availability of methanol and ethylene glycol testing. Gas chromatography can reliably quantify the presence of ethylene glycol or methanol, but most hospitals are unable to obtain these tests in a timely fashion [112]. Moreover, some hospitals offer a "toxic alcohol screen" that detects methanol, ethanol, and isopropanol but not ethylene glycol, which is a diol. This nomenclature can mislead a clinician into interpreting a negative "toxic alcohol screen" as excluding the presence of ethylene glycol. Interference due to propionic acid, propylene glycol, glycerol, 2,3-butanediol, and β-hydroxybutyrate has been described [113–116]. Testing for glycolic acid or formic acid is even less available [76,117,118]. A rapid bedside qualitative test for ethylene glycol is available but not approved for diagnostic use in humans [119]. Breath alcohol analysis can mistake methanol for ethanol, providing indirect evidence of exposure. Therefore, diagnostic and therapeutic decisions are often based on circumstantial evidence derived from the history and available laboratory testing, pending confirmatory testing. It is essential for the physician to understand the strengths and the limitations of these indirect markers of toxicity.

Arterial pH measurements in ethylene glycol exposed patients can range from 6.7 to 7.5 [62,103]. Ethylene glycol poisoning often results in higher anion gaps than other causes of this abnormality [64]. A gap of 58 has been reported [70]. The differential diagnosis of an increased anion gap metabolic acidosis is discussed above (see Alcoholic Ketoacidosis section). In young children, child abuse and inborn errors of organic acid metabolism should be considered in the differential diagnosis [116,120]. Hyperkalemia may be seen in association with acidosis and with renal failure [61,78,101]. The creatinine and blood urea nitrogen are normal unless renal failure has supervened. Calcium levels are initially normal but may drop significantly as calcium complexes with oxalic acid to form calcium oxalate. The electrocardiogram may show ST-T wave and QTc changes consistent with hypocalcemia, hyperkalemia, or both.

The osmol gap (refer to Chapters 71, 101, and 117) is frequently used as a diagnostic test in the evaluation of these patients. Extreme caution must be used when interpreting the osmol gap, however. First, the serum osmolality should be measured by the freezing point depression, as vapor pressure osmometry will not detect methanol, ethanol, and isopropanol [121].

Although an osmol gap greater than 10 mOsm is often sought as indirect evidence of the presence of an exogenous alcohol or glycol, *failure to find an elevated osmol gap does not rule out significant alcohol or glycol ingestion* [122]. Cumulative measurement error in the formula parameters, variations in the formula itself, and the natural variability in the osmol gap at baseline contribute to imprecision in the calculated osmol gap [52,123,124]. This variability can hide a significant amount of an alcohol or glycol. Furthermore, as the parent

alcohol or glycol is oxidized to the toxic charged metabolite, the osmol gap disappears. Conversely, an elevated osmol gap is not specific for alcohols or glycols, as lactic acidosis, ketoacidosis, and sepsis can also increase the osmol gap [122].

In studies of various control populations not exposed to methanol, isopropanol, or ethylene glycol, osmol gaps averaged approximately −1 to −2 mOsm per kg [125–127]. The variability was substantial, however, with standard deviations of between 5 and 8 mOsm per kg. Thus, although an arbitrary upper limit of 10 mOsm per kg has historically been used for the normal osmol gap [128], an osmol gap of 10 mOsm per kg in a patient whose usual baseline gap is 0 could represent substantial serum concentrations of ethylene glycol (62 mg per dL) or methanol (32 mg per dL) [129]. One patient with an osmol gap of only 11 mOsm per kg had an ethylene glycol level of 38 mg per dL and subsequently developed renal failure [64], whereas another patient with an osmol gap of 7.2 mOsm per kg required hemodialysis for ethylene glycol toxicity [130]. Thus, an elevated osmol gap may suggest the presence of an alcohol or glycol, but a normal gap does not rule out a small ingestion or a late presentation [122,126,131,132].

Microscopic examination of the urine for crystals is another indirect diagnostic test frequently recommended. Less than 50% of patients have crystalluria at presentation, however. Sequential urinalysis may improve sensitivity in detecting crystalluria [60,67,133]. Calcium oxalate monohydrate (needle shaped) and calcium oxalate dihydrate (envelope shaped) crystals can be seen. The monohydrate crystals are the predominant form at all concentrations and are more specific for ethylene glycol toxicity, but may be confused with uric or hippuric acid crystals [64,67]. The dihydrate crystals tend to occur at higher concentrations and convert to the monohydrate form within 24 hours [134]. They are less specific and can also be found in the urine after ingestion of oxalate-containing foods such as rhubarb. Other nonspecific urinary findings can include low specific gravity, proteinuria, hematuria, and pyuria. Some antifreeze manufacturers add fluorescein to their products to facilitate the detection of radiator leaks. Wood's lamp examination of the urine or gastric aspirate to detect fluorescence is unreliable and should not be used to make or exclude the diagnosis [135,136]. Other drugs, food products, toxins, and even endogenous compounds cause urine to fluoresce, as do many urine collection containers themselves [137,138].

Methanol

The laboratory studies listed for ethylene glycol evaluation should be obtained. Methanol can also cause an anion gap metabolic acidosis and an osmol gap [109]. The caveats noted under ethylene glycol for the evaluation and interpretation of these parameters apply equally to methanol. Elevated lactate levels, mild hypokalemia, and leukocytosis may occur. Lactic acidosis may be seen late in the course of methanol poisoning and may result from inhibition of the mitochondrial electron transport system or from poor tissue perfusion [73]. Serum lactate concentrations of 11.5 and 23 mmol per L have been reported 24 hours or more after ingestion. Amylase elevations and pancreatitis can occur in up to one half of severely poisoned patients [10,100]. Computed tomography scanning can demonstrate cerebral edema, as well as frontal lobe and basal ganglia hemorrhages and infarcts associated with poor clinical outcomes.

Management

The focus of treatment for ethylene glycol and methanol poisoning is to prevent the formation of toxic metabolites by inhibiting liver ADH and enhancing the removal of the parent compound and metabolites. Antidotal therapy, cofactor therapy, and hemodialysis may be necessary in addition to supportive care to achieve these goals.

Initial treatment includes airway management in the comatose patient, IV fluids, cardiac monitoring, and appropriate laboratory studies. Gastric aspiration via a nasogastric tube may be beneficial when performed within an hour of an intentional ingestion [83]. Oral activated charcoal is ineffective but may be considered when coingestants are suspected [81,139].

IV sodium bicarbonate should be administered to correct serum pH to at least 7.3 [100,139]. Large doses of sodium bicarbonate may be required. Sodium bicarbonate is useful in ethylene glycol and methanol poisonings for three reasons. First, unlike the metabolites in lactic acidosis and ketoacidosis, the metabolites of ethylene glycol and methanol cannot be transformed to regenerate bicarbonate [64], and the acidosis must be corrected with exogenous alkali. Second, increasing the serum pH enhances the ionization of acid metabolites, making them less diffusible, trapping them in the blood and extracellular fluid, and limiting their tissue penetration [73]. Third, urinary alkalinization may increase excretion of acid metabolites through ion trapping, provided renal function remains normal [67]. In ethylene glycol poisoning, however, the hypocalcemia that occurs as calcium complexes with oxalate may be worsened by alkali administration. Calcium chloride/gluconate should be administered to correct symptomatic hypocalcemia including seizures, but the indiscriminate use of calcium salts to correct a laboratory value should be avoided, because it may increase the precipitation of calcium oxalate crystals [140]. In methanol poisoning, increasing the serum pH may increase the concentration of ionized formate, thus diminishing formic acid access to the CNS and possibly ameliorating retinal toxicity [73].

Seizures should initially be treated with standard anticonvulsants, such as benzodiazepines and barbiturates. Hypocalcemia and hypoglycemia should be excluded. Recurrent or persistent coma or seizures should prompt evaluation for underlying cerebral edema. Cerebral edema should be managed acutely with hyperventilation, mannitol (provided renal function is intact), and potentially intracranial pressure monitoring and decompression. Cardiopulmonary complications may require inotropes and vasopressors.

Ethanol and fomepizole are antidotes for ethylene glycol and methanol poisoning. These agents inhibit liver ADH, and block the initial oxidation of ethylene glycol and methanol to their more toxic metabolites. After ADH is inhibited, ethylene glycol and methanol can be eliminated via endogenous or extracorporeal routes [85,141]. Antidotal therapy has no effect on the elimination of the acid metabolites. Indications for antidotal therapy in cases of known or possible methanol or ethylene glycol intoxication are outlined in Table 119.3 [101,103,139,142].

Recognition that ethanol is the preferred substrate for ADH [143] suggested its clinical use as a competitive inhibitor of this enzyme [144]. While most sources recommend administering sufficient ethanol to maintain serum ethanol concentrations between 100 and 150 mg per dL [97], limited data support this target concentration. Because ethanol is a competitive inhibitor of ADH, extremely high levels of ethylene glycol or methanol must by necessity be met with higher doses of ethanol. Targeting a 1:4 molar ratio [73,143] a serum ethanol concentration of 100 mg per dL should suffice for methanol concentrations as high as 257 mg per dL or ethylene glycol as high as 540 mg per dL. Dosage guidelines to achieve an ethanol concentration of 100 mg per dL are outlined in Table 119.4 [84,145].

There are disadvantages to using ethanol therapeutically [81,146,147]. Perhaps the most important limitation is the toxicity of ethanol itself, including coma, airway compromise, respiratory depression, and agitation [30,148,149]. At

TABLE 119.3

INDICATIONS FOR ALCOHOL DEHYDROGENASE INHIBITOR THERAPY

A serum methanol or ethylene glycol concentration > 20 mg/dL[a]

When serum methanol or ethylene glycol levels are not readily available:
- Documented ingestion of a consequential amount of methanol or ethylene glycol, especially when it is associated with a falling serum bicarbonate level or serum osmol gap > 10 mOsm/kg by freezing point depression
- History or strong clinical suspicion of methanol or ethylene glycol ingestion and one of the following:
  - A falling serum bicarbonate level or a serum bicarbonate < 20 mmol
  - Arterial pH < 7.3
  - Renal dysfunction or ocular toxicity

[a] Attempts should be made to obtain confirmatory methanol or ethylene glycol concentrations as soon as possible when contemplating alcohol dehydrogenase inhibitor therapy. In all cases, consultation with a medical toxicologist is strongly recommended.

recommended doses, ethanol induces inebriation in the nontolerant individual. Subsequent behavioral effects and severe mental status depression may require interventions, such as sedation and endotracheal intubation shortly after initiation of therapy. The need for these interventions as well as the continuous infusion of ethanol itself can complicate and delay interfacility transfer. Although IV ethanol administration is generally preferred over oral ethanol, this requires extemporaneous compounding from dehydrated ethanol and an infusion of a hypertonic solution (10% ethanol by volume is 1,700 mOsm per kg), usually via a central venous catheter. Maintaining an adequate ethanol level can be difficult and interindividual variation in metabolism and removal during hemodialysis necessitate frequent monitoring of serum concentrations and dosage adjustments [148]. Finally, ethanol therapy is relatively contraindicated in patients on disulfiram or similar medications, patients with hepatic disease, and patients with alcohol addiction [81]. Admission to an intensive care setting is considered mandatory for an individual receiving ethanol therapy.

Given these limitations to ethanol therapy, fomepizole has emerged as the preferred antidote. A more potent competitive inhibitor of ADH [67,140,150–154], parenteral fomepizole is approved by the U.S. Food and Drug Administration for therapy of methanol and ethylene glycol poisoning in adults [130,142,155,156]. Fomepizole has many advantages over ethanol: wide therapeutic margin, ease of administration, fixed dosing schedule, lack of CNS or behavioral toxicity, lack of metabolic or fluid balance effects, patient and provider safety, and no need for drug concentration monitoring [81,146,147,149,154]. Currently, fomepizole is only available in a parenteral formulation, though oral administration of this same formulation has similar pharmacokinetics and efficacy [157]. Highly selected patients treated with fomepizole may also avoid hemodialysis (discussed later), intensive care unit admission, or even interfacility transfer [67,79,81,146,151,156–160]. These advantages are even more important in the setting of mass epidemics [95].

A minimum serum fomepizole concentration of 10 μM (0.8 mg per dL) [161] effectively halts ethylene glycol and methanol oxidation [79,103,142,153,162] and is much higher than the in vitro K_i of fomepizole for human ADH of 1 μM [163]. Recommended dosing (Table 119.5) achieves and maintains serum fomepizole concentrations greater than 100 μM, eliminating the need for drug concentration monitoring [164]. Adverse drug events associated with fomepizole therapy are infrequent, but include rash, eosinophilia, minimal hepatic transaminase elevations, nausea, vomiting, and abdominal pain [148,165]. Hypersensitivity to pyrazoles, such as celecoxib and zaleplon, is the only contraindication to its use. Fomepizole does not appear to affect retinol dehydrogenases

TABLE 119.4

ETHANOL DOSING FOR ETHYLENE GLYCOL OR METHANOL POISONING

Loading dose of ethanol:
- 0.8 g/kg (1 mL/kg) of 100% ethanol
- Oral or via nasogastric tube: Use 20%–30% concentration (e.g., 5 mL/kg of 20% ethanol; recall "80 proof" = 40% by volume)
- Intravenous: use 5%–10% concentration, load over 1 h (e.g., 10 mL/kg of 10% ethanol in D_5 W over 1 h)

If ethanol is already present, the amount of ethanol required to achieve a serum ethanol level of 100–150 mg/dL may be calculated as follows:
- Amount ethanol (mg) = [desired concentration (mg/dL)—known concentration (mg/dL)] × V_d of ethanol (0.6 L/kg) × body weight (kg) × 10 dL/L

Maintenance doses of ethanol:
- Begin during administration of the loading dose.
- Give 80 mg/kg/h of ethanol orally or intravenously (as above). For a patient on hemodialysis, the maintenance dose should be higher: 250–350 mg/kg/h. Chronic alcoholics also require higher doses (average 150 mg/kg/h). Because of potential hypoglycemia, glucose should be given along with ethanol. Serum ethanol and glucose levels must be monitored frequently.

D_5 W, dextrose 5% in water; V_d, volume of distribution

[a] Adapted from Ekins BR, Rollins DE, Duffy DP, et al: Standardized treatment of severe methanol poisoning with ethanol and hemodialysis. *West J Med* 142:337, 1985.

TABLE 119.5

FOMEPIZOLE INTRAVENOUS DOSING PROTOCOL

Loading dose: 15 mg/kg

Maintenance dose (beginning 12 h after loading dose):
- 10 mg/kg every 12 h; increase dose to 15 mg/kg every 12 h if more than 48 h after loading dose

Dosing during hemodialysis:
- At initiation of dialysis:
  - If < 6 h since last dose, no additional dose
  - If > 6 h since last dose, next scheduled dose
- During hemodialysis: next scheduled dose every 4 h
- At completion of hemodialysis:
  - If < 1 h since last dose, no additional dose
  - If 1–3 h since last dose, half of next scheduled dose
  - If > 3 h since last dose, next scheduled dose

Each dose diluted in 100 mL normal saline and infused over 30 min

involved in vision [166,167]. Its dosing protocol is based on zero-order elimination kinetics, increased clearance during hemodialysis, and potential auto-induction of metabolism via cytochrome P450–2E1 [130,154,155,168,169] (Table 119.5).

The main disadvantage to fomepizole therapy is the higher acquisition cost of the drug compared to ethanol [170,171], although this acquisition cost must be balanced against improved patient safety and reduced intensity of monitoring and therapy [146,159,172]. Although there are no prospective clinical studies directly comparing the safety of ethanol with fomepizole, a recent hospital record review reported far fewer adverse drug events with fomepizole [184]. In this study, the *number needed to harm* with ethanol was only two, and only seven when restricted to severe harm (mostly coma, violent agitation, and hemodynamic instability) [149]. Fomepizole is the antidote of choice, when available [171], especially for a patient who has coingested other CNS depressants, for the critically ill patient with a profound anion gap metabolic acidosis of uncertain etiology, for the patient in whom hemodialysis may be technically challenging (e.g., infants), and during times of limited resources as may occur during mass poisonings [81,147,173].

Fomepizole has also been successfully used to treat combined methanol/isopropanol [174] and diethylene glycol/triethylene glycol [158] overdose in humans. Treatment with fomepizole or ethanol should be continued until the metabolic acidosis has resolved and serum methanol or ethylene glycol levels fall below 20 mg per dL.

Cofactor therapy in patients poisoned by ethylene glycol includes IV pyridoxine (100 mg) and thiamine (100 mg) once a day until ethylene glycol levels are unmeasurable and acidemia has cleared. Pyridoxine is required for the conversion of glyoxylic acid to glycine, whereas thiamine and magnesium are required for the conversion of glycolic acid to γ-hydroxy-α-ketoadipate. Administering these cofactors may shunt metabolism away from the formation of oxalic acid [60,61], although benefit has not been documented in human poisonings. Magnesium should be administered to patients with hypomagnesemia.

Patients poisoned with methanol should receive IV folinic acid (leucovorin), 1 to 2 mg per kg every 4 to 6 hours until methanol and metabolic acidosis have been cleared [90,140]. Folic acid (folate) can be substituted if leucovorin is unavailable. Hepatic formate metabolism occurs through a folate-dependent mechanism (see Fig. 119.5). The susceptibility of primates to methanol toxicity correlates with reduced hepatic 5,6,7,8-tetrahydrofolate (THF, or reduced folate) stores compared with lower mammals [140], and exogenous folinic acid (5-formyl-THF) or folate may increase their capacity to remove formate. Although human data are limited, monkeys pretreated with folic or folinic acid resulted in marked attenuation of serum formate levels and metabolic acidosis after methanol administration [175]. Folinic acid given after the onset of methanol toxicity was also beneficial.

Hemodialysis effectively removes ethylene glycol, methanol, glycolic acid, formic acid, and probably the other toxic metabolites, and should be used in nearly all cases with acidosis or end-organ toxicity [66,79,89,97]. Early hemodialysis can prevent subsequent toxicity [21,134]. Addition of extra sodium bicarbonate to the dialysate can assist in correcting acidosis, and hemodialysis may assist in controlling volume status. The frequency of fomepizole dosing must be increased during hemodialysis to compensate for its removal. When using ethanol, its infusion rate should be empirically doubled at the start of hemodialysis, and serum ethanol levels should be monitored hourly.

Recommendations for hemodialysis are outlined in Table 119.6 [79,82,85,140,146,147]. Traditional criteria for hemodialysis have included a serum ethylene glycol or methanol concentration greater than 50 mg per dL, independent of symptoms, acid–base status, or other markers of end-organ toxicity [140]. Selected patients have been successfully managed with fomepizole, cofactors, and IV fluid hydration alone despite serum ethylene glycol concentrations >400 mg per dL, though consultation with a toxicologist is strongly recommended [153,159,176,177]. Such patients must be hemodynamically stabile, and have near normal acid–base status and renal function. If minimal ethylene glycol metabolism has occurred before initiation of fomepizole therapy, the endogenous ethylene glycol elimination half-life is expected to be less than 18 hours [79]. Thus, patients with a normal serum creatinine and arterial pH at the start of fomepizole therapy may forgo hemodialysis despite high serum ethylene glycol concentrations [79,81,160]. Although a similar strategy has been reported in a patient with combined methanol/isopropanol ingestion [174], the prolonged methanol elimination half-life (approximately 50 hours) after ADH inhibition [178] would favor hemodialysis when readily available and technically feasible. Acid–base status, renal function, and serum ethylene glycol or methanol levels must be closely monitored in patients in whom hemodialysis is withheld [146].

Ethylene glycol clearance rates of 156 to 226 mL per minute (fractional excretion 43% to 92%; half-life 2.3 to 3.5 hours) can be expected during hemodialysis, as compared with renal clearance rates of 27.5 ± 4.1 mL per minute (fractional excretion 26% ± 9%) in patients with normal renal function, and clearance rates of 1 to 6 mL per minute in patients with renal dysfunction [79,80]. Glycolic acid is removed by hemodialysis, with a clearance of 105 to 170 mL per minute (half-life 2.5 hours) [62,64,68]. The hemodialysis elimination rate for methanol is 142 to 286 mL per minute; for formate, it is 148 to 203 mL per minute [20,89,97,101,145].

Hemodialysis should be continued until serum ethylene glycol or methanol levels are below 20 mg per dL and acid–base derangement has been corrected [73,81]. The required duration of hemodialysis in hours can be estimated using the formula $[-V \ln (20/A)/0.06\,k]$, where V is total body water in liters, A is the initial alcohol concentration in mg per dL, and k is 57% of the dialyzer urea clearance in milliliters per minute at the observed blood flow rate [179–181]. More than one round of hemodialysis may be necessary in massive overdoses and for ethylene glycol poisoned patients with renal failure.

TABLE 119.6

INDICATIONS FOR HEMODIALYSIS IN METHANOL OR ETHYLENE GLYCOL POISONING

Renal dysfunction as evidenced by increased serum creatinine concentration[a]
Severe metabolic acidosis (pH < 7.25) with evidence of end-organ toxicity (abnormal renal function for ethylene glycol, visual toxicity for methanol) independent of parent compound concentration
Serum methanol or ethylene glycol concentration > 50 mg/dL

[a] Selected patients with ethylene glycol concentrations above 50 mg/dL *and* normal creatinine and arterial pH at initiation of fomepizole treatment may be eligible for conservative treatment without hemodialysis. In all cases, consultation with a medical toxicologist is strongly recommended.

Adapted from Barceloux DG, Krenzelok EP, Olson K, et al: American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *J Toxicol Clin Toxicol* 37:537, 1999.

Peritoneal dialysis is markedly inferior to hemodialysis. Continuous arteriovenous hemofiltration with dialysis has been used in a hemodynamically unstable patient, but is less efficient at toxin removal [182]. Sorbent-based hemodialysis systems were inadvertently shown to be ineffective for methanol removal due to rapid saturation of the sorbent cartridge [183] and charcoal cartridges saturate within a few hours [175].

Patients with ethylene glycol poisoning who have acute renal failure may require hemodialysis for several months. Recovery of renal function is the expected course, although renal dysfunction may be permanent [61,62,67,73,83,184]. Full neurologic recovery is possible even after prolonged coma and seizures. Transient cranial nerve palsies developing 4 to 18 days after ingestion have been reported in under- or untreated patients [80,105–107]. Bilateral basal ganglia and brainstem infarction can occur in severely ethylene glycol poisoned patients [185].

Seizures, coma, and severe acidosis in patients with methanol poisoning portend a poor prognosis [109]. Cerebral edema is a common postmortem methanol toxicity finding [160]. The development of dilated, unresponsive pupils may indicate either severe optic nerve damage or cerebral edema [110]. Other neurologic sequelae include a parkinsonian-like syndrome, spasticity, transient resting tremor, cognitive defects, and paraplegia. Computed tomography, magnetic resonance, and autopsy studies have documented frontal lobe and basal ganglia hemorrhages and infarcts, especially in the putamen [186–191]. Bilateral putaminal hemorrhage and/or insular subcortex white matter necrosis correlate with a poor clinical outcome following methanol toxicity. The etiology of these lesions remains uncertain, but they are likely due to the direct toxicity of methanol and/or its metabolites. These abnormalities usually occur in severely acidemic patients with delayed presentation or diagnosis.

Harvesting of organs for transplant is not precluded in patients who die from ethylene glycol or methanol poisoning. Several centers have reported successful experience with kidney, heart, lung, pancreatic beta cell, and liver procurement from methanol-poisoned patients [172,192–196].

ISOPROPANOL

Isopropanol (isopropyl alcohol) is a clear, colorless, volatile liquid with a disagreeable taste and characteristic odor [197]. It is commonly available over the counter in 70% solutions of "rubbing alcohol." Because of its ready availability at an inexpensive price, abusers of alcohol often ingest isopropanol as an ethanol substitute. Cases of toxicity have been reported in children who were sponge bathed with the compound [198,199].

Isopropanol produces CNS depression, coma, and death from respiratory depression. In this respect, it has twice the potency of ethanol [200,201], a phenomenon attributed to its higher molecular weight [197] and possibly the CNS depressant effects of its metabolite, acetone. Depending on individual tolerance, serum concentrations of 150 mg per dL or greater may induce coma, and levels of 200 mg per dL or greater can be fatal in untreated patients, although lower concentrations may produce severe adverse effects [202].

The chemical properties and kinetics of isopropanol are summarized in Table 119.1. Oral absorption usually occurs within 30 minutes. Eighty percent of an absorbed dose is oxidized to acetone via ADH (Fig. 119.6) [197,201]. Acetone cannot undergo further oxidation to a carboxylic acid, however. Therefore, metabolic acidosis is not a feature of isopropanol toxicity unless respiratory depression with hypoxia or

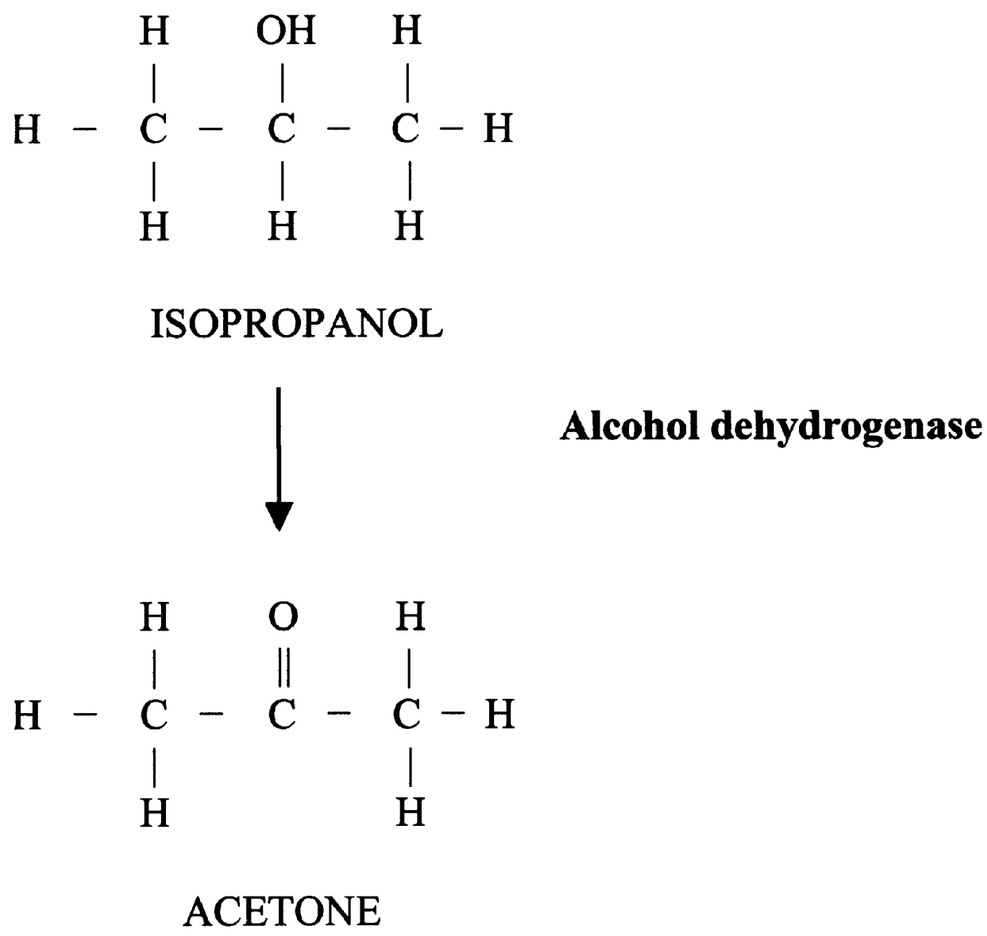

FIGURE 119.6. Isopropanol metabolism.

hypotension results in lactate production. Excretion of acetone and unchanged isopropanol (20% of an absorbed dose) is predominantly renal, with some excretion by respiratory, gastric, and salivary routes [201]. Acetone can be detected in the urine within 3 hours of ingestion [203]. The elimination half-life of isopropanol can be as long as 5.8 hours in infants [204]. Serum acetone levels frequently remain elevated after isopropanol levels are undetectable because acetone is eliminated slowly, with a half-life of 10.8 to 31.0 hours. The contribution of acetone to the prolonged duration of CNS depression remains speculative [197].

Clinical Presentation

An "intoxicated" patient without acidemia, yet with positive serum or urinary ketones and a fruity breath odor, should be suspected of isopropanol intoxication. Initial signs and symptoms usually consist of mild intoxication followed by gastritis, abdominal pain, nausea, vomiting, and possibly hematemesis [197]. Hemorrhagic tracheobronchitis may occur. As CNS depression progresses, patients become ataxic, dysarthric, confused, stuporous, and comatose. Pupils are typically miotic, but mydriasis has been reported [197,198,205,206]. Respiratory depression and hypotension may occur in severe intoxication [207]. Because of the profound and prolonged cerebral depressive effects of isopropanol, comatose patients may develop compartment syndromes and rhabdomyolysis with myoglobinuria. Delayed hypoglycemia may occur via the mechanism described for ethanol [197,198,202].

Many patients who ingest isopropanol are ethanol abusers who have a multitude of associated diseases, including chronic liver disease, pancreatitis, traumatic injuries, and chronic obstructive pulmonary disease, which may complicate the clinical picture.

Diagnostic Evaluation

Patients with known or suspected isopropanol poisoning should have quantitative isopropanol and acetone serum levels

along with the laboratory studies noted for acute ethanol intoxication. The presence of high levels of acetone can interfere with older creatinine assays based on a colorimetric method, producing a falsely high creatinine value in the presence of a normal BUN [208,209]. In patients who may have also ingested other toxic alcohols, serum osmolality, ethanol, ethylene glycol, and methanol levels should also be obtained.

The differential diagnosis of isopropanol poisoning includes toxic and metabolic states in which ketonemia may develop, such as alcoholic, diabetic, and starvation ketoacidosis. Patients with these conditions have elevated acetoacetate, β-hydroxybutyrate, and acetone levels compared with the isolated acetonemia seen with isopropanol intoxication. Traces of isopropanol may be detected in patients with diabetic or AKA due to the back reduction of acetone to isopropanol [210,211]. Poisoning by salicylate, cyanide, and acetone itself (which is found in nail polish and super glue remover) and inborn errors of metabolism should also be considered in the differential diagnosis of unexplained ketosis. Some degree of metabolic acidosis is expected in most of these conditions, whereas it is absent in uncomplicated isopropanol or acetone poisoning cases.

Management

Treatment is similar to that described for acute ethanol intoxication. Airway management and evaluation for hemorrhagic gastritis are particularly important. IV fluids should contain glucose, and serum glucose levels should be periodically checked. Isopropanol and acetone are removed by hemodialysis, but such therapy is rarely indicated [205]. Occasionally, patients with serum isopropanol concentration greater than 400 mg per dL accompanied by hemodynamic instability despite IV fluids may benefit from hemodialysis [197]. Since acetone is less toxic than isopropanol, there is no indication for either fomepizole or ethanol therapy [174,212].

Most patients recover with appropriate airway management and treatment of complicating factors. CNS depression and volume depletion secondary to vomiting can cause hypotension [197]. Pulmonary edema and hemorrhage are common findings on autopsy [202] and should be anticipated in severely ill patients.

PROPYLENE GLYCOL

Propylene glycol (1,2-propanediol) is commonly used as a solvent (e.g., in laundry stain removers), as an antifreeze, and as a diluent for a number of pharmaceuticals, including IV formulations of chlordiazepoxide, lorazepam, diazepam, etomidate, phenobarbital, pentobarbital, phenytoin, procainamide, nitroglycerin, and theophylline and topical silver sulfadiazine cream. Oral and dermal absorption is usually poor, but toxic amounts may be absorbed through abraded or burned skin [213]. Approximately one-half of a dose undergoes hepatic oxidation via ADH to lactate, and then to pyruvate and acetate. The rest is excreted unchanged in the urine [214].

Although oral doses of as much as 1 g per kg are essentially nontoxic, toxicity can occur following rapid or prolonged infusion of higher doses. Rapid IV infusion, as might occur during phenytoin loading, can cause prolonged PR and QRS duration, idioventricular rhythms, and cardiorespiratory depression and arrest [215]. Infusion of smaller doses has also precipitated cardiac standstill [216]. Propylene glycol, rather than phenytoin, is responsible for such toxicity [215]. Elderly patients, especially those with severe underlying cardiac disease, are at increased risk and should be infused with medications containing propylene glycol at rates slower than those usually recommended.

Alternatively, frequent repeat IV dosing of medications using propylene glycol as a diluent, as might occur with extremely high doses of diazepam for ethanol withdrawal, massive ingestion of products containing propylene glycol, or the chronic dermal absorption of silver sulfadiazine through damaged skin, can lead to accumulation of propylene glycol and its metabolites, resulting in seizures, and decreased level of consciousness [217–219]. On laboratory testing, an osmolar gap and high serum lactate concentrations are expected. Propylene glycol can be mistaken for ethylene glycol on gas chromatography [220].

Management consists of immediately stopping IV infusion or dermal application and supportive therapy. Fomepizole has been used to block the metabolism of propylene glycol, but this therapy cannot be recommended in the absence of information on the relative toxicity of the parent compound to its metabolites [221]. Hemodialysis and continuous venovenous hemofiltration have reportedly been used to treat patients with propylene glycol toxicity [222,223].

DIETHYLENE GLYCOL

Diethylene glycol (2,2′-dihydroxydiethyl ether, ethylene diglycol, 2,2′-oxydiethanol, 3-oxapentane-1,5-diol; DEG) is a viscous and sweet tasting liquid found in resins, antifreeze, brake fluids, cosmetics, wallpaper strippers, inks, lubricants, liquid heating/cooking fuels, plasticizers, adhesives, paper, and packaging materials [12,224]. Over the years, diethylene glycol has resulted in tragic outbreaks of renal failure and death following its substitution for propylene glycol in medications [225,226]. Unlike propylene glycol, diethylene glycol can cause acute renal failure, elevated liver enzymes, encephalopathy, and delayed neurologic toxicity. Since the first reported outbreak that occurred in the United States in 1937, there have been other outbreaks worldwide, including South Africa (1969), Spain (1985), India (1986 and 1998), Nigeria (1990 and 2008), Bangladesh (1990 to 1992), Argentina (1992), Haiti (1996), Panama (2006), and China (2006). These outbreaks often involved medications, such as acetaminophen, cough syrup, or teething syrup, ingested by children. The number of identified deaths during each outbreak ranged from 5 to 236. The median toxic dose is estimated to be approximately 1 g per kg [227].

Following diethylene glycol ingestion, patients may present with gastrointestinal symptoms, inebriation, CNS depression, acidosis, and renal failure. Interestingly, additional neurologic symptoms may develop up to several weeks after the ingestion and include cranial nerve palsy, peripheral neuropathy, dysphonia, lethargy, mental status changes, quadriparesis, and seizures [225,228]. Metabolism of diethylene glycol via hepatic ADH leads to 2-hydroxyethoxyacetic acid (2-HEAA) [224]. Although 2-HEAA is believed to be the primary toxic metabolite, the parent glycol itself may also be directly toxic. Although the name suggests the potential to be metabolized to two ethylene glycol molecules, this does not occur in vivo [224]. Survivors with renal failure tend to remain dialysis dependent and the degree of renal injury may be a predictor of delayed neurologic sequelae. Treatment is similar to ethylene glycol, including ADH inhibition, extracorporeal elimination, and supportive care. Fomepizole without hemodialysis, however, is not recommended given the uncertain toxicity of the diethylene glycol itself [159,224,225].

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CHAPTER 120 ■ ANTIARRHYTHMIC AGENTS

MICHAEL GANETSKY

The therapeutic use, misuse, and intentional overdose of antiarrhythmic drugs are associated with severe morbidity and mortality [1]. The recognition, management, and prevention of antiarrhythmic toxicity require an understanding of the pharmacology of these drugs as they are related to cardiac electrophysiology. A general review of the mechanisms involved as well as the principles of management of poisoning is followed by a discussion of individual agents.

PHARMACOLOGY

Antiarrhythmic drugs are most commonly classified on the basis of their predominant physiologic effect and mechanism of action as originally proposed by Vaughan Williams [2] and Campbell [3] (Tables 120.1 and 120.2; Fig. 120.1).

The major effect of class I agents is blockade of the fast inward sodium current responsible for the rapid upstroke and conduction of the action potential [4] (see Fig. 120.1). This effect is also known as *local anesthetic* or *membrane stabilizing action*. Class I drugs depress automaticity, particularly in Purkinje fibers. Class I drugs comprise a large group of antiarrhythmic agents, many of which have diverse electrophysiologic properties; consequently, this class has been subdivided into classes IA, IB, and IC (see Table 120.2) [3].

The class II antiarrhythmic drugs are β-adrenergic antagonists; they inhibit the proarrhythmic effects of catecholamines, which shorten refractory periods and facilitate reentrant circuits. The slowly conducting, calcium-channel–dependent action potentials of the normal sinoatrial (SA) and atrioventricular (AV) nodes (see Fig. 120.1) rely partially on sympathetic tone. Class II drugs depress conduction and automaticity through these specialized tissues, leading to bradycardia and AV block. Toxicity due to beta-blockers is covered further in Chapter 125.

Class III agents prolong the refractory period by increasing the cardiac action potential duration (APD), especially in phases 2 and 3 (see Fig. 120.1). This effect is produced by blockade of the major outward potassium-rectifying (repolarizing) current. Amiodarone is the prototypic class III agent, whereas ibutilide and dofetilide are newer class III agents.

Class IV drugs (calcium antagonists or calcium channel blockers) antagonize the slow inward calcium current responsible for the slow upstroke and conduction of the action potentials of SA and AV nodal cells [4] (see Fig. 120.1). Verapamil, diltiazem, and nifedipine represent the three subclasses of calcium channel antagonists. Both verapamil and diltiazem have negative inotropic and chronotropic properties and are useful for slowing the ventricular response rate in patients with atrial

TABLE 120.1

VAUGHAN WILLIAMS CLASSIFICATION OF ANTIARRHYTHMIC ACTIONS

Class	Drugs	Actions
I	Quinidine Procainamide Disopyramide Moricizine Lidocaine Tocainide Mexiletine Flecainide Propafenone	Block fast sodium current (hence slow conduction)
II	Beta-blockers	Block effects of catecholamines
III	Amiodarone Sotalol Ibutilide Bretylium	Prolong action potential and, hence, refractoriness by blocking K^+ current
IV	Verapamil Diltiazem	Block cardiac calcium channel

TABLE 120.2

SUBGROUPS OF CLASS I DRUGS

Class	Drugs	Effects on action potential	Summary of clinical effects
IA	Quinidine Procainamide Disopyramide Moricizine	Reduce rate of depolarization; prolong duration of action potential	Moderate slowing of cardiac conduction; prolongation of refractory periods
IB	Lidocaine Mexiletine Tocainide	Reduce rate of depolarization selectively in ischemic cells; shorten action potential duration	Selective depression of ischemic tissue; may shorten refractory periods
IC	Flecainide Propafenone	Marked depression of depolarization rate	Marked slowing of cardiac conduction; small increase in refractory periods

fibrillation. In therapeutic dosing, calcium channel antagonists such as nifedipine have little effect on cardiac conduction or inotropic state and are, therefore, not used for their antiarrhythmic properties. Calcium channel blocker toxicity is discussed in Chapter 126.

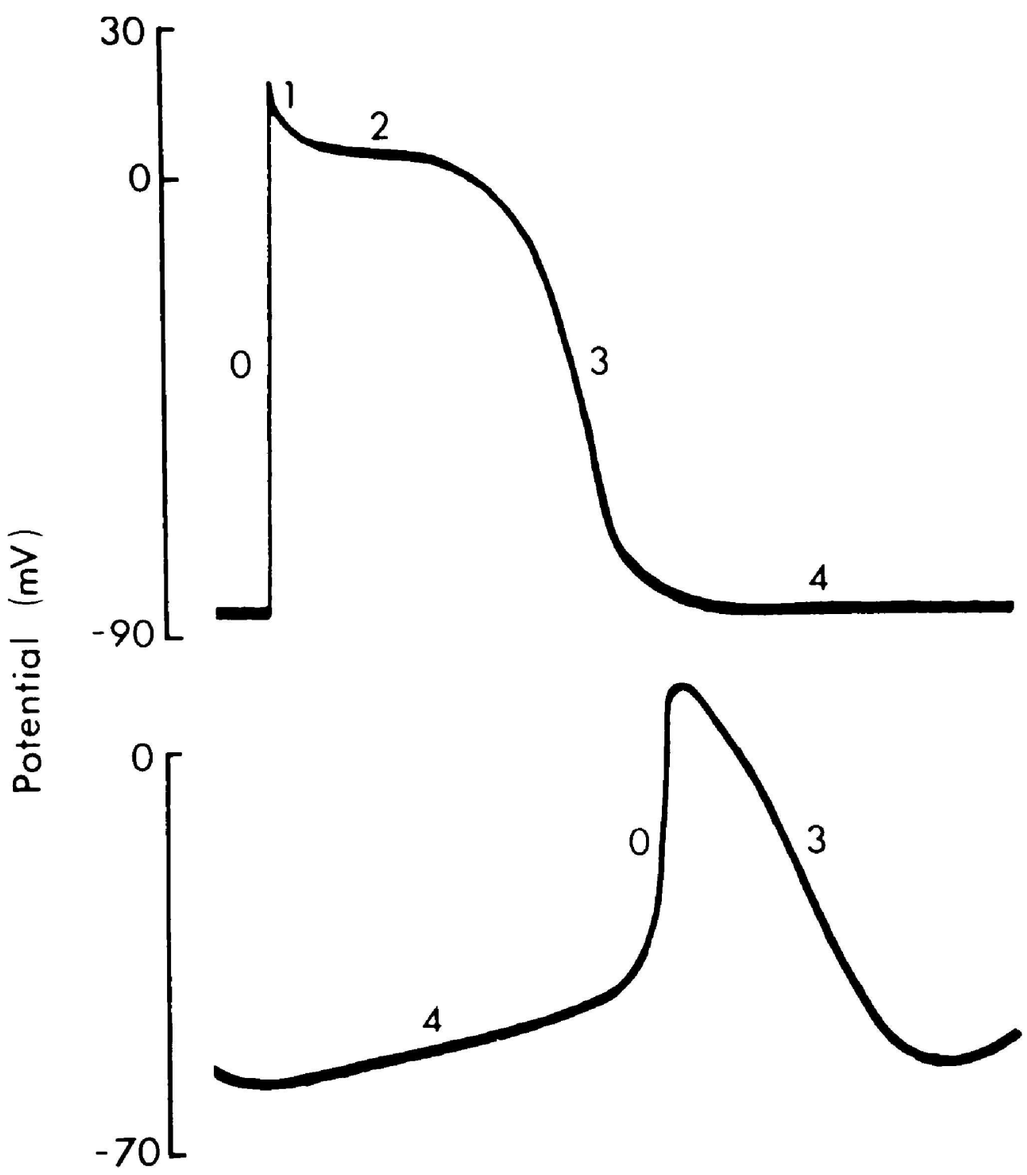

FIGURE 120.1. Typical cellular action potentials recorded from working myocardium (*upper trace*) and the atrioventricular node (*lower trace*). The nodal cell has an action potential of smaller amplitude, with a much slower rate of depolarization in phase 0. The nodal cell exhibits spontaneous diastolic (phase 4) depolarization ("pacemaker" activity). Rapid depolarization in phase 0 (atrial and ventricular cells and Purkinje fibers) is produced by a fast inward sodium current (depressed by class I drugs). A slower inward calcium current is also present but is the only inward current found in sinoatrial and atrioventricular nodal cells. This explains their slower rate of depolarization in phase 0 and their sensitivity to calcium-channel blockers. Repolarization (phase 3) is produced by a number of outward potassium currents; the rapid component of the delayed rectifier potassium current is the most important. Blockade of this current by antiarrhythmic or other drugs prolongs repolarization and action potential duration (class III action).

Adenosine and digoxin are two drugs with antiarrhythmic effects that do not fall within the Vaughan Williams classification. Adenosine is an endogenous nucleoside that produces AV nodal conduction block and vasodilation via specific adenosine-sensitive receptors. The antiarrhythmic properties and toxicity of digoxin are discussed in Chapter 127.

The cellular electropharmacology of antiarrhythmic agents involves suppression of automaticity, decreased cardiac conduction, and refractory period prolongation. Automaticity, the spontaneous depolarization of pacemaker myocytes, occurs in SA and AV nodes as well as in Purkinje fibers. In SA and AV nodal cells, the rate of firing depends on several different inward and outward currents; the combination of currents renders these cells relatively insensitive to depression by antiarrhythmic drugs [1,4,5]. In Purkinje fibers, however, automaticity occurs as an escape phenomenon that arises in the presence of AV block. Escape beats probably result from the action of a single inward sodium channel (the "pacemaker current") and are suppressed by therapeutic concentrations of most class I antiarrhythmic agents. Therefore, Purkinje fiber automaticity is more susceptible to depression by antiarrhythmic agents than is sinus node automaticity. Nonetheless, clinical suppression of the sinus node leading to asystole, particularly in the presence of the high vagal tone commonly seen in the early phases of acute myocardial infarction, is an uncommon but well-recognized complication of therapy with antiarrhythmic agents such as lidocaine.

Reentrant circuit arrhythmias depend on conduction rates around the circuit and the refractory periods of pathway components. If the conduction time falls below the refractory period of part of the circuit, the "excitable gap" disappears, the advancing wavefront meets only refractory tissue, and the arrhythmia terminates. An ideal antiarrhythmic agent would, therefore, accelerate conduction and prolong refractoriness within the substrate for reentry. Many antiarrhythmic agents prolong refractory periods in myocardium, but none accelerates conduction in therapeutic use. Almost invariably, conduction tends to slow. This combination of decreasing conduction and refractory period prolongation can be either proarrhythmic or antiarrhythmic [5]. However, clinicians cannot predict which outcome is likely for a given drug in a given patient. Some antiarrhythmic agents (in particular, class IB drugs and amiodarone [3]) show selectivity for depressing conduction in ischemic or otherwise abnormal myocardium by binding preferentially to the inactivated state of the sodium channel. A complete conduction block through an ischemic segment of a reentrant circuit may be the mechanism of arrhythmia termination; this could occur without slowing conduction in healthy myocardium. Other drugs tend to show less selectivity and depress conduction in normal myocardium at therapeutic

concentrations, probably explaining the greater propensity of class IC drugs to be proarrhythmic both in therapeutic use and in overdose [3].

Although most antiarrhythmic agents prolong refractoriness, lidocaine, mexiletine, and tocainide tend to shorten it, particularly in low concentrations; this may explain some cases of drug-associated arrhythmogenesis in patients with reentrant tachycardias. Lengthening of refractoriness should be proarrhythmic, but if conduction is slowed simultaneously, the net effect on the reentrant circuit determines the outcome.

Antiarrhythmic drugs suppress most forms of automaticity known to cause tachyarrhythmias. The major exception to this rule is the form of triggered automaticity due to *early after-depolarizations* (EADs). EADs can be defined as a marked slowing of repolarization, visible on the action-potential recording and due to reduction of the normal repolarizing outward potassium current. If voltage conditions are appropriate, prolonged depolarization may trigger a series of automatic action potentials. The upstrokes of these action potentials are due to inward current flow through the normal calcium channels that had been inactivated, had recovered from inactivation, and had found the membrane potential still within their activation range. The channels then reactivate and produce a secondary upstroke. Increased intracellular calcium concentrations activate calcium-sensitive potassium channels and accelerate repolarization. This process can occur as a single event or as an oscillatory series of action potentials, depending on the prevailing conditions of voltage and calcium levels [6–8].

The induction of EADs may be the basis of arrhythmias, including torsade de pointes associated with long QT syndromes [5,6,9]. According to this theory, the slowing of repolarization leads directly to the QT wave prolongation, often with associated prominent, bizarre TU waves. Any triggered activity, should it occur, results in ventricular tachyarrhythmias.

The class IA antiarrhythmic agents quinidine, disopyramide, and procainamide are all capable of producing EADs and torsade de pointes [6]. This is also true of the class III drugs, such as amiodarone, sotalol, ibutilide, and dofetilide. The class IB agents, lidocaine, mexiletine, and tocainide, do not produce EADs and do not cause torsade de pointes. Class IC compounds infrequently cause significant slowing of repolarization and have not been shown to cause torsade de pointes. Of the class IV agents, only mibefradil has an effect on repolarization, which usually manifests as TU-wave changes. Experimental models suggest that this effect is not proarrhythmic; however, there has been a report of torsade due to QT prolongation from therapeutic dosing of mibefradil [10,11].

CLINICAL PRESENTATION

Toxicity common to therapeutic doses and overdoses of antiarrhythmic agents include depression of automaticity and cardiac conduction, which may be caused by a combination of direct electrophysiologic and secondary metabolic effects. Symptoms following acute overdose usually begin within 4 hours and can occur at any time during chronic therapy. Drug absorption may continue for many hours following the ingestion of large doses, sustained-release preparations, or agents with anticholinergic effects, resulting in delayed or progressive toxicity. Respiratory depression and hypotension produce acidosis and myocardial ischemia that further aggravate depressed conduction. Cardiac manifestations include QRS prolongation, QTc prolongation, sinus node dysfunction, bradycardia, AV block, ventricular arrhythmias, and poor ventricular function. These derangements can culminate in intractable arrhythmias, cardiogenic shock, or death. Manifestations of acute toxicity may also include dizziness, visual disturbances, psychosis, anticholinergic symptoms, hypoglycemia, hyperglycemia, and hypokalemia. Seizures may result from class I (particularly IB) toxicity. Procainamide and quinidine can cause hypotension if infused too rapidly.

Warning signs that indicate an increased risk of torsade include a QTc interval greater than 560 milliseconds, previous history of torsade, bradycardia, increased frequency and complexity of ventricular premature beats, or a ventricular premature beat falling on the T wave [12].

The electrocardiogram (ECG) may provide a clue to the agent or class involved in cases where the drug ingested is not known. Class IB drugs usually have no effect on the QT interval; whereas class IA, IC, and III agents prolong it. With class IA agents, QT prolongation is due to slowing of both depolarization and repolarization. Hence, both the QRS duration and JT interval are increased. In contrast, QT prolongation primarily results from slowed depolarization with class IC agents, resulting in an increased QRS (but not JT) duration and from prolonged repolarization with class III agents, resulting in an increased JT (but not QRS) interval.

The differential diagnosis of bradyarrhythmias includes beta-blocker, calcium channel blocker, cholinergic agent (carbamate and organophosphate insecticides), clonidine, cyclic antidepressant, and digitalis poisoning. Other agents that cause QRS and QT interval prolongation include antihistamines, antipsychotic agents, cyclic antidepressants, magnesium, and potassium. Ventricular tachyarrhythmias may occur in poisoning with sympathomimetics (see Chapter 144). Hypoglycemia, hypoxia, and metabolic disturbances should be considered in the differential diagnosis of patients with neurologic symptoms.

DIAGNOSTIC EVALUATION

Physical examination should focus on vital signs and respiratory, cardiovascular, and central nervous system (CNS) function. Frequent vital signs and continuous cardiac monitoring should be performed. Essential tests include an ECG and serum electrolytes, blood urea nitrogen, creatinine, and magnesium measurement; liver function tests and serum drug levels, if available, may also be helpful. A chest radiograph should be obtained as clinically indicated. Patients with hypotension and hypoxemia should have arterial blood gas and serum lactate measurements.

MANAGEMENT

The general features of antiarrhythmic drug overdose and their management are discussed below (Table 120.3). Care of the antiarrhythmic poisoned patient centers on general supportive and critical care principles. Unique aspects pertinent to individual drugs are discussed in later sections. All patients suspected of ingesting an overdose of antiarrhythmic agents should receive oral activated charcoal. Patients with complications of therapeutic dosing may also benefit from oral activated charcoal to reduce absorption of a recently administered drug dose. The greatest amount of absorption to charcoal will occur if given within 1 to 2 hours of ingestions. CNS and respiratory depression commonly require airway support by endotracheal intubation. Seizures are managed by benzodiazepine therapy. Phenytoin should never be used to treat seizures secondary to drug toxicity because of the risk of increased mortality.

Initial therapy for hypotension involves administration of intravenous fluids. Because poisoned patients are infrequently hypovolemic, fluid administration should be monitored closely. In general, if a response in blood pressure is not seen with 2 L of intravenous fluids, pressors such as norepinephrine should be administered. Early consideration should be given to

TABLE 120.3

MANAGEMENT OF LIFE-THREATENING ANTIARRHYTHMIC DRUG OVERDOSE

Supportive care
Activated charcoal for acute (< 1 h) oral ingestions
Correct acidosis, hypoxia
Benzodiazepines for seizure control
Enhance drug elimination
Activated charcoal
Consider extracorporeal elimination if appropriate
Hypotension
Fluid administration
Alkalinization (hypertonic $NaHCO_3$) for class I drugs
Inotropes, vasopressors
Consider pulmonary artery catheter for monitoring
Circulatory assist devices
Impaired conduction
Temporary pacing for atrioventricular block or bradycardia
Alkalinization (hypertonic $NaHCO_3$) for class I drugs
Ventricular arrhythmias
Torsade de pointes
Temporary pacing
$MgSO_4$
Isoproterenol
Monomorphic ventricular tachycardia
Cardioversion, if causing hypotension
Hypertonic $NaHCO_3$ for class I drugs
Lidocaine, except for class IB drugs
Overdrive pacing
PEA cardiac arrest
Intravenous lipid emulsion for bupivacaine (may consider for other lipophilic agents or in refractory cases). Loading dose of 1.5 mL/kg administered over 1 min, repeated one to two times every 3–5 min as needed. If hemodynamic improvement is noted, the loading dose should be followed by a continuous infusion at a rate of 0.25–0.5 mL/kg/min

circulatory assist devices for patients with cardiogenic shock. Intra-aortic balloon pump counterpulsation has been used successfully to treat patients with severe quinidine or disopyramide toxicity [13,14], and partial cardiac bypass has been used to maintain circulation during massive lidocaine or flecainide toxicity [15–17].

Decreased ventricular conduction, as measured by QRS prolongation in quinidine, procainamide, flecainide, and encainide toxicity, are often treated with sodium bicarbonate infusion [18–22]. In animals, hypertonic sodium bicarbonate reverses ventricular arrhythmias caused by flecainide toxicity [23] and reverses hypotension due to tricyclic antidepressants with class IA antiarrhythmic effects [20]. Hypertonic sodium bicarbonate should be considered for the treatment of QRS widening greater than 100 milliseconds or ventricular tachyarrhythmias in the setting of class IA or IC drug toxicity. Common practice is to administer intravenous boluses of sodium bicarbonate (50 mEq of 1 mEq per mL solution) as needed to increase and maintain blood pH between 7.45 and 7.55. As an alternative, a continuous infusion of 1,000 mL of 5% dextrose in water containing 2 to 3 amps of sodium bicarbonate and potassium chloride is an option. Bicarbonate should be administered for 12 to 24 hours and then gradually withdrawn while watching for QRS lengthening to recur. At present, there is no evidence that prophylactic alkalinization before QRS widening changes outcome. In the most severely poisoned patients, however, alkalinization may be ineffective, especially if there is persistent metabolic acidosis. In a series of patients with class I antiarrhythmic drug overdose requiring cardiopulmonary resuscitation, only 2 of 29 survived despite the use of hypertonic sodium bicarbonate [24].

Sodium bicarbonate appears to act by increasing the extracellular sodium concentration and reducing the drug-induced sodium channel blockade [25]. Hypertonic sodium chloride has proven effective in animals and, anecdotally, in humans, but sodium bicarbonate is generally preferable because increasing pH is equally or more important in some models [20,25–27] (see Chapter 123 for more detail).

The treatment of recalcitrant ventricular tachycardia typically consists of repeated cardioversions, cardiopulmonary resuscitation, vasopressor support, and mechanical ventilation. Treatment with other class IA and IC antiarrhythmic drugs is contraindicated, given the potential for further arrhythmia aggravation [28]. Lidocaine may be considered because it does not depress conduction, but it is often ineffective. Suppression of ventricular tachycardia and hemodynamic improvement has been anecdotally described with sodium bicarbonate [21,22]. Overdrive pacing may also be effective.

The treatment of torsade de pointes should include 1 to 2 g of a 25% solution of intravenous magnesium sulfate. Direct-current cardioversion is often effective in terminating torsade de pointes, but it frequently recurs. Increasing the ventricular rate to greater than 90 to 110 beats per minute by an infusion of isoproterenol or ventricular pacing may also be effective [29,30]. In one study, infusion of potassium chloride at 0.5 mEq per kg for 60 to 90 minutes normalized excessive quinidine-induced QT prolongation, but simply correcting hypokalemia did not suppress torsade de pointes [31]. Lidocaine is inconsistently effective [32,33]. Treatment with class IA or III antiarrhythmic drugs is contraindicated because further prolongation of repolarization and the QT interval may exacerbate torsade de pointes. Magnesium therapy should also be considered in patients at increased risk for this arrhythmia (see earlier); it has been found to prevent occurrence of torsade in a dog model (dose of 30 to 60 mg per kg) [34].

Although most antiarrhythmic drugs are weak bases, urine acidification is contraindicated because systemic acidosis may aggravate cardiotoxicity [20]; treatment with hypertonic alkaline solution to reduce cardiotoxicity is likely to be of greater benefit. Hemodialysis is of limited benefit for antiarrhythmic toxicity because drug clearance is limited by protein binding and high lipid solubility [26,35,36]. Hemoperfusion using charcoal resin is more effective in removing drugs with high protein binding and high lipid solubility; however, this modality is rarely available. Hemoperfusion is of greatest value for disopyramide [37] or *N*-acetylprocainamide (NAPA) toxicity [38].

INDIVIDUAL AGENTS

Class IA Agents

Quinidine

Quinidine is administered orally as sulfate or gluconate. The usual dose of immediate-release quinidine sulfate is 200 to 400 mg, four times per day, with gluconate doses being approximately 30% higher. Bioavailability is approximately 70% for both forms; peak plasma levels are reached earlier for the sulfate (60 to 90 minutes) than for the gluconate. Quinidine is metabolized by CYP3A4 to 3-OH quinidine and

TABLE 120.4

DOSE AND PHARMACOKINETICS OF CLASS I AND II ANTIARRHYTHMIC AGENTS

Drug	Usual daily dose	Therapeutic or usual plasma concentration (μg/mL)	Volume of distribution (L/kg)	Elimination half-life	% Excreted unchanged in Urine	% Bound in plasma	Active metabolites	Methods of enhancing elimination
Class IA								
Quinidine	Depends on formulation (see text)	2–7	2.0–3.5	7 h	17–50[a]	80–90	3–OH quinidine	—
Procainamide	3–6 g	4–8 (NAPA, 7–15)	2 (NAPA, 1.4)	2.5–4.5 h (NAPA, 5–9 h)	40–60 (NAPA, 80)	10–20 (NAPA, 10)	NAPA	HD, HP
Disopyramide	300–600 mg	2–6	1.0–1.5	4–10 h	40–60	50–65	—	HD, HP
Moricizine	600–900 mg	0.1–3.0[b]	8–11	1.5–13.0 h	1	95	—	—
Class IB								
Lidocaine	1–3 μg/min	1.5–6.0	1.0–1.7	1.5–2.5 h[c]	< 10	60–80	Monoethylglycinexylidide, glycine xylidide	?HP
Tocainide	1.2–2.4 g	3–10	1.5–3.2	11–20 h	40	10	—	HD, HP
Mexiletine	600–1,200 mg	0.5–2.0	5–7	6–17 h	8–15	50–70	—	—
Class IC								
Flecainide	100–300 mg	0.07–0.50	9	12–18 h[a,d]	70	50	—	—
Propafenone	400–800 mg	0.2–1.8	1.9–3.0	3.6 h (17 h)[e]	—	—	5–hydroxypropafenone	—
Class III								
Amiodarone	100–400 mg	1.0–2.5[b]	70	40–49 d	< 1	99	Desethylamiodarone	—
Sotalol	160–320 mg	0.6–3.2	2	12–15 h	> 75	0	—	HD, HP
Bretylium	See text	?	7	4–10 h	95	1–6	—	—

[a] Shorter with lower urine pH.
[b] Correlates poorly with therapeutic effect.
[c] Longer in patients with congestive heart failure.
[d] Dose dependent.
[e] Slow metabolizers at CYP2D6 locus.
HD, hemodialysis; HP, hemoperfusion; NAPA, *N*-acetylprocainamide.

quinidine-*N*-oxide; these metabolites have less electrophysiologic activity than quinidine [39,40]. Details of pharmacokinetics are listed in Table 120.4.

Torsade de pointes is an adverse effect of therapeutic doses of quinidine (also known as *quinidine syncope*). Risk factors for this arrhythmia are recent initiation of quinidine therapy, concurrent digoxin therapy, female gender, structural heart disease, hypokalemia, and hypomagnesemia. Possible mechanisms include prolongation of the QTc interval and potentiation of EADs [40].

In therapeutic doses, sustained-release quinidine formulations produce therapeutic plasma concentrations for up to 8 hours in most patients. In overdose, however, saturation of enzymes that metabolize the drug may dramatically prolong serum concentrations. Consequently, serial serum drug monitoring is warranted (see Table 120.4), especially when potentially interactive agents, are coadministered. Agents that are CYP3A4 inhibitors, such as cimetidine, can increase quinidine serum concentration. Mild quinidine overdose presents as cinchonism (headache, tinnitus, deafness, diplopia, confusion), vertigo, visual disturbances (blurred vision, photophobia, scotomata, contracted visual fields, yellow vision), or delirium. Severe toxicity is characterized by CNS toxicity (lethargy, coma, respiratory depression, seizures), gastrointestinal tract toxicity (nausea, vomiting, diarrhea), and cardiovascular collapse [41]. Noncardiac side effects include nausea, cinchonism, thrombocytopenia, and drug-induced fever.

Initial therapy for acute quinidine overdose should include gastric decontamination with activated charcoal. Treatment of CNS toxicity is supportive, with intubation and ventilation for CNS depression and benzodiazepines for seizures. Deaths from quinidine overdose are usually secondary to arrhythmias or hypotension. When pacing is indicated for bradycardia, failure to capture is common in the face of drug-induced myocardial depression. QRS prolongation should be treated with bicarbonate infusion. Hypotension may result from vasodilation from β-adrenergic blockade, impaired contractility from sodium channel blockade, or arrhythmias. Vasodilation may be treated with fluid administration and alpha-acting vasopressors such as norepinephrine; large doses may be required.

Refractory hypotension has been successfully treated with an intra-aortic balloon pump [13] and partial circulatory bypass.

Procainamide

Procainamide is eliminated by hepatic metabolism and renal excretion [42,43]. The major metabolite is NAPA, which has potent class III and some class I antiarrhythmic activity [44]. In fast acetylators or in renal failure, as much as 40% of a dose of procainamide may be excreted as NAPA. Because the prevalence of the fast and slow acetylator phenotypes varies between ethnic groups, widely variable procainamide and NAPA concentrations may occur in specific populations [45]. Blood concentrations of NAPA may exceed those of the parent drug, given its dependence on renal elimination.

The cardiovascular side effects of procainamide are very similar to those of quinidine except that the drug has no β-adrenergic antagonist activity. Acute procainamide toxicity is manifested primarily by hypotension, but QRS widening and ventricular arrhythmias may also occur [46]. Inappropriate drug dosing in renal insufficiency or before achieving steady-state concentrations is the most common cause of procainamide toxicity. Toxic levels of NAPA (> 25 µg per mL) may begin to accumulate as a result of acute or chronic renal insufficiency, potentially leading to torsade. Approximately 40% of patients receiving long-term oral therapy with procainamide develop a syndrome resembling systemic lupus erythematosus that usually resolves after drug withdrawal [47].

Signs and symptoms of acute procainamide overdose are similar to those of quinidine overdose. Patients with non–life-threatening procainamide toxicity (e.g., hypotension) and adequate renal function can be managed with supportive care. Seizure has been reported in a pediatric ingestion [48]. Hypertonic sodium bicarbonate may be useful for QRS prolongation, monomorphic ventricular tachycardia, or hypotension [18]. This therapy has minimal benefit in NAPA toxicity because this metabolite has primarily class III effects. Torsade de pointes should be treated as already discussed. Anecdotal reports have showed increased procainamide and NAPA clearance with hemodialysis or hemoperfusion; however, clinical significance is unclear [38,46].

Disopyramide

Disopyramide, unlike most other antiarrhythmic drugs, has protein binding that shows nonlinear, saturable characteristics [49,50]. This is clinically important because small increases in total plasma level within the therapeutic range (see Table 120.3) may mask larger rises in free (active) drug concentration. When administered intravenously, disopyramide produces hypotension less frequently than do quinidine or procainamide. Widening of the QRS complex, prolongation of the QT interval, and drug-induced ventricular tachyarrhythmias have all been reported as side effects [51]. There are numerous reports of QTc prolongation, torsade, or monomorphic ventricular tachycardia from the interaction of disopyramide and macrolide antibiotics. Erythromycin, clarithromycin, and azithromycin have all been implicated; a possible mechanism is inhibition of hepatic CYP3A4 [52].

Acute disopyramide overdose is similar to that of quinidine or procainamide, with QRS prolongation, severe refractory hypotension, and arrhythmias [14,53–55]. Hypoglycemia is a recognized adverse effect [55]. Data regarding management are limited, but an approach similar to that for quinidine toxicity is appropriate. Hypotension refractory to intravenous fluids and vasopressors has been treated with an intra-aortic balloon pump [14]. Because of its relatively small volume of distribution, disopyramide clearance is substantially increased by hemoperfusion [14,37,56].

Class IB Agents

Lidocaine (and Other Local Anesthetics)

Amide-type local anesthetics (e.g., articaine, bupivacaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine) are extensively metabolized by hepatic dealkylation, hydrolysis, ring hydroxylation, and conjugation. Ester-type agents are metabolized by hepatic and plasma esterases. Derivatives of para-aminobenzoic acid (e.g., benzocaine, procaine, tetracaine) are predominantly hydrolyzed by plasma pseudocholinesterase, whereas other esters (e.g., cocaine, dyclonine, proparacaine) are predominantly metabolized in the liver [57]. Allergic cross-reactivity occurs within the amide and ester groups but not between them.

Extensive first-pass metabolism prevents effective oral therapy with lidocaine and local anesthetics, but toxicity can occur after ingestion [57]. The maintenance infusion rate of lidocaine must be reduced in patients with cardiac failure or hepatic dysfunction and in the elderly [58]. Plasma concentrations should be monitored for infusions lasting longer than 24 hours. Lidocaine has two active metabolites, monoethylglycinexylidide (MEGX) and glycine xylidide (GX). Although these metabolites have short elimination half-lives of 2 hours and 1 hour, respectively, they may contribute significantly to toxicity, which can occur several hours after an infusion is started [57,58]. Most lidocaine toxicity is caused by errors in dosing and administration [59]. Life-threatening toxicity and death have occurred after inadvertent overdose, surgical procedures such as liposuction, and parenteral, mucosal, and topical anesthesia [60–62]. The safety of tumescent liposuction, in which large volumes of lidocaine solutions are infused subcutaneously, has been called into question following several reported deaths [63].

All local anesthetics have toxicity similar to lidocaine, with neurologic signs and symptoms usually preceding cardiac manifestations, except in massive acute overdose [64,65]. Neurologic symptoms, the most significant of which is seizures, include auditory disturbances, visual disturbances, paresthesias, and ataxia. Lidocaine has a bimodal concentration-dependent effect on seizures; lidocaine suppresses seizures at concentrations between 0.5 and 5 µg per mL but increases the risk at levels above 8 to 9 µg per mL. The relative contribution to epileptogenicity of the parent compound compared with the metabolites MEGX and GX is still unclear [66]. Adverse cardiac effects from lidocaine administration are unusual in the absence of severe underlying conduction-system disease, acute myocardial ischemia, or massive overdose. Persons with third-degree heart block requiring ventricular arrhythmia suppression should have a prophylactic pacemaker inserted before lidocaine administration [67]. However, lidocaine administration in asymptomatic patients with bundle-branch block or intraventricular conduction disease carries a low risk [68].

Acute massive overdose of lidocaine is characterized by seizures, coma, respiratory arrest, and cardiovascular collapse [61,64,69–71]. Hypotension is due to myocardial depression [72]. Lidocaine has little or no effect on the QT interval; however, QRS prolongation, AV block, and depressed automaticity with bradycardia or asystole can occur. Data regarding management are anecdotal. Seizures should be managed using intravenous diazepam; phenytoin should be avoided. Bradyarrhythmias may respond to isoproterenol infusion or cardiac pacing. Hypotension and shock respond to fluid administration and vasopressors such as dopamine. If QRS prolongation is present, hypertonic sodium bicarbonate may be useful. Intra-aortic balloon pump and cardiopulmonary bypass have been used successfully in patients with circulatory collapse [15,16].

Amide-type local anesthetics can also induce methemoglobinemia [57,70,73]. This effect has been described after

percutaneous absorption of benzocaine-containing formulations, during use of prilocaine as an epidural anesthetic agent, and due to prilocaine found in eutectic mixture of local anesthetics (EMLA) cream. Amide agents are hydrolyzed to an amino group that exerts an oxidizing stress in susceptible individuals—such as those with G-6-PD deficiency—to produce methemoglobinemia. In some cases, patients may also exhibit red blood cell hemolysis. Methemog-lobinemia is treated with methylene blue (see Chapter 147).

Bupivacaine intoxication can lead to PEA cardiac arrest that is not responsive to standard ACLS protocols. This is a dreaded complication of regional anesthesia after inadvertent intravenous injection of bupivacaine. Intravenous lipid emulsion (Intralipid) is rapidly becoming accepted as standard treatment for bupivacaine-induced cardiac arrest. Even though no human trials exist, there is excellent animal evidence and several human case reports [74]. The mechanism is still unclear, but effects are likely from partitioning of bupivacaine away from cardiac receptors and into an intravenous lipid phase. Therefore, intralipid may be an effective therapy for other lipophilic anesthetic agents. The initial loading dose is 1.5 mL per kg (typically 100 mL in an average adult) administered over 1 minute, which can be repeated one to two times every 3 to 5 minutes. If hemodynamic improvement is noted, the loading dose should be followed by a continuous infusion at a rate of 0.25 to 0.5 mL per kg per minute [75].

Tocainide

Adverse effects are common during tocainide therapy, with up to 50% of patients requiring dosage adjustments or discontinuation [76]. The most common side effects are nausea, vomiting, and anorexia, and neurologic effects such as dizziness, paresthesias, tremor, ataxia, and confusion. Tremor suggests that the maximum tolerable dose of tocainide has been reached. Serious toxicity resulting from pulmonary fibrosis in up to 0.1% and agranulocytosis and leukopenia in 0.2% of patients has been reported [77]. Monitoring for clinical or laboratory signs of agranulocytosis has been recommended, particularly during the first 12 weeks of therapy.

Massive tocainide overdose causes effects similar to those of lidocaine overdose: loss of consciousness, seizures, high-degree AV block, asystole, and ventricular fibrillation [76,78–80]. Treatment considerations are also similar. Because 40% of tocainide elimination is renal, urine acidification theoretically increases tocainide excretion but is not recommended because of enhanced systemic toxicity.

Mexiletine

Mexiletine is structurally similar to lidocaine and undergoes extensive metabolism in the liver to largely inactive compounds [81,82]. Hepatic impairment can significantly prolong the elimination half-life to 25 hours or longer. Patients with chronic liver disease, such as hepatic cirrhosis, undergo a marked reduction in the hepatic metabolism of mexiletine [83,84]. Smoking enhances mexiletine elimination, reducing the half-life by 35% compared with nonsmokers [85]. Phenytoin, rifampin, and phenobarbital induce hepatic enzymes and lower mexiletine plasma concentrations. Antacid therapy, cimetidine, and narcotic analgesics can slow the absorption of mexiletine [86].

Mexiletine is generally well tolerated, with little effect on hemodynamics, even in patients with congestive heart failure [87]. Mexiletine shares much of the side effect profile of lidocaine, including cross-reactivity in allergic individuals. Dizziness, ataxia, and tremor are relatively common. Overdose effects resemble those of lidocaine. Heart block or asystole accompanied by hypotension occur with massive overdose [88,89]. Status epilepticus requiring diazepam and phenobarbital has been described [90]. The prolonged duration of seizures compared with lidocaine overdose may be due to mexiletine's longer elimination half-life of 5.5 to 12 hours. A urine drug immunoassay was reported as positive for amphetamines in the setting of a mexiletine overdose, likely from cross-reactivity due to structural similarity of these compounds [91].

Class IC Agents

Flecainide

Flecainide is very well absorbed orally, with negligible hepatic first-pass effect. Flecainide displays polymorphic drug metabolism because it is metabolized via CYP2D6 to active metabolites. This phenomenon effectively results in two distinct populations of patients having very different clearance rates. The average half-life is between 8 and 10 hours, with substantial individual variability. Inhibitors of the CYP2D6 pathway, such as INH, quinidine, selective serotonin-uptake inhibitors, and other agents metabolized by this pathway, may decrease or increase the clearance of flecainide when added to or deleted from therapy. Amiodarone can double the serum concentration of flecainide when the two drugs are concomitantly administered; the flecainide dose should be reduced by 50% when these drugs are coadministered. Serum concentrations can be followed but are rarely used. The proposed therapeutic range is 200 to 1,000 ng per mL.

Flecainide is approved for the management of paroxysmal atrial fibrillation or flutter associated with disabling symptoms, but there are many restrictions due to its adverse effects. Flecainide has a very narrow therapeutic index and can be toxic even at therapeutic concentrations [92]. In the Cardiac Arrhythmia Suppression Trial (CAST) [93], postinfarction patients being treated for ventricular arrhythmias demonstrated an increased mortality relative to patients treated with placebo. Furthermore, flecainide possesses considerable negative inotropic effects that limit its usefulness in the setting of congestive heart failure. Other dose-related side effects occur, including CNS toxicity such as blurred vision, dizziness, headache, nausea, and paresthesias. Flecainide also increases the ventricular pacing threshold.

Flecainide is highly toxic in overdose; in one series, the mortality rate was 10% [24]. Overdose is characterized by QRS prolongation with a normal JT interval, hypotension, coma, or seizures [24,94]. Serious cardiac effects that can occur include severe bradycardia, high-grade conduction blocks, and ventricular dysrhythmias. Cardiac arrest is not uncommon after overdose; survival after full arrest is rare [92]. Data regarding management are mostly anecdotal. In rats, hypertonic sodium bicarbonate, 3 to 6 mEq per kg, reduced flecainide-induced QRS prolongation [95], and in dogs, this treatment largely abolished ventricular tachycardia [23]. In overdose patients, both hypertonic sodium bicarbonate and sodium lactate have been reported to be effective [96,97]. Hypertonic sodium bicarbonate or sodium lactate should be considered in patients with evidence of disturbed ventricular conduction. Cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO) have been used to support perfusion until spontaneous perfusion returned [17,98]. In one report, a patient who developed refractory ventricular fibrillation due to a flecainide overdose was successfully resuscitated after a 300-mg amiodarone bolus was given [92].

Propafenone

Propafenone is used for select patients with atrial fibrillation and for refractory ventricular tachycardia and fibrillation. Like flecainide, propafenone undergoes significant first-pass hepatic metabolism via the CYP2D6 isoenzyme pathway.

Bioavailability ranges from 5% to 50%, depending on the patient's phenotype; agents that inhibit CYP2D6 lower the clearance rate. Administering propafenone with food may significantly increase bioavailability in extensive metabolizers by diminishing first-pass drug extraction [99,100].

Propafenone has other drug interactions as well. Propafenone administration may increase digoxin concentrations between 35% and 85% due to impairment of nonrenal digoxin clearance. Quinidine is a specific and potent inhibitor of CYP2D6 and can significantly increase propafenone concentration [101]. Coadministration of propafenone with warfarin may result in a 25% increase in prothrombin time from unknown mechanisms. Similar to flecainide, propafenone has a narrow therapeutic index.

Propafenone overdose is similar to that of flecainide; toxicity includes QRS prolongation, hypotension, bradycardia, coma, and seizures [24,102,103]. Seizures appear to be more common in propafenone overdose than in flecainide overdose. PR interval prolongation is a characteristic finding in propafenone toxicity [104,105]. Hypertonic sodium bicarbonate has been beneficial for QRS prolongations and aberrant ventricular conduction [106,107]. Benzodiazepines should be used for seizures; phenytoin should be avoided [108]. Management of cardiovascular toxicity is similar to that of flecainide overdose. Transvenous cardiac pacing was successful in a case with severe bradycardia due to a high-grade conduction block [104].

Class III Agents

Amiodarone

Amiodarone was first used as a vascular smooth-muscle relaxant. In addition to its class III activity (prolonging the cardiac APD), amiodarone possesses properties common to all Vaughan Williams classifications. These include calcium channel–smooth-muscle relaxant (class IV), noncompetitive antiadrenergic (class II), and some sodium-channel–blocking (class I) activity.

Amiodarone is generally considered the most effective antiarrhythmic agent for treatment and prophylaxis of most types of arrhythmia [109]. Its clinical use, however, is complicated by unusual pharmacokinetics (see Table 120.4) and prevalent side effects [110,111]. After oral administration, amiodarone widely distributes into body tissues where drug concentration generally exceeds that of the plasma. It is highly lipophilic, highly bound to plasma proteins, and has an extremely long (average, 53 days) elimination half-life [112]. Metabolism occurs in the liver and possibly in the gastrointestinal tract. The major metabolite, desethylamiodarone, accumulates in plasma and tissues and has electrophysiologic properties that are similar to the parent compound [113,114].

Many side effects are dose dependent, but therapeutic drug monitoring is of little benefit, except to determine compliance. Evidence suggests a limited correlation between drug level and antiarrhythmic effect [115] and serious noncardiac toxicity seems to be more likely at levels above 2.5 µg per mL [116,117].

Pulmonary fibrosis is an important and potentially life-threatening side effect of long-term therapy [118]. Pulmonary toxicity is somewhat dose dependant; its prevalence ranges from 5% to 15% in patients who take at least 500 mg per day, but is 0.1% to 0.5% when the dose is less than 200 mg per day [119]. Common presenting features include dyspnea, nonproductive cough, fever, and general malaise. A diffuse interstitial pattern on the chest film, similar to congestive heart failure, is the most typical radiographic finding. Symptoms usually resolve with withdrawal of amiodarone therapy. Corticosteroids may improve prognosis and prevent relapse [119].

Amiodarone generally does not produce congestive heart failure, even in patients with poor ventricular function, because its vasodilator properties may offset negative inotropic effects. Sinus bradycardia is common during therapy, and symptomatic sinus pauses or sinus arrest can occur in 2% to 4% of patients. AV block may occur in patients with underlying conduction-system disease. Torsade de pointes has been reported, but is much less likely than with other class III agents.

Amiodarone is iodinated and interferes with conversion of thyroxine to triiodothyronine, causing significant elevations of thyroxine and slight reductions in triiodothyronine concentrations [120]. Most patients are typically euthyroid, with normal thyroid stimulating hormone levels. Peripheral neuropathy, tremor, and nervousness develop initially in up to 30% of patients, but these symptoms often improve over time. Asymptomatic corneal microdeposits are present in almost all patients on long-term therapy. Dermatologic effects include increased photosensitivity and blue-gray skin discoloration.

Asymptomatic elevation of hepatic transaminase is relatively common with long-term amiodarone therapy; the reported incidence is 24% to 26%. Transaminase can reach up to 3 times normal and resolve with or without discontinuation of therapy [121]. Acute hepatitis following intravenous loading of amiodarone is much less common but not infrequently described in the literature [121,122]. Transaminitis can be severe and rarely lead to fatality. Postulated mechanisms include a polysorbate 80 additive used in the intravenous preparation, immunologic-mediated injury, or a direct hepatotoxic effect [123].

Acute amiodarone overdoses generally tend to follow a benign course. There are several reports of ingestions developing self-limited episodes of ventricular tachycardia, QT prolongation, or mild bradycardia [124,125]. No CNS depression or seizures have been reported. Cholestyramine modestly reduces the elimination half-life of amiodarone from 44 to 28 days, perhaps by interrupting enterohepatic recirculation [126]. There is likely a role for multidose activated charcoal, even up to 12 hours after the ingestion, since amiodarone has delayed an erratic enteral absorption [127].

Sotalol

Sotalol is a β-adrenergic antagonist with class III activity. It is used for the prophylaxis and treatment of AV reentrant and ventricular tachycardias. It has excellent oral bioavailability and is mostly renally excreted unchanged. Overdoses manifest both pharmacologic properties of sotalol; β-adrenergic antagonism causes bradycardia, hypotension, low cardiac output, and CNS depression, while the class III activity causes QT prolongation, ventricular ectopy, and dysrhythmias, especially torsade de pointes. Reported cases of ventricular arrhythmias due to sotalol overdose are typically associated with bradycardia [127]. Management should include treatment of the beta-blocker toxicity (see Chapter 127 for discussion) and control of QT prolongation and torsade de pointes with agents such as magnesium or isoproterenol (see earlier for further discussion). There are reports of lidocaine suppressing torsade from sotalol overdose [127,128].

Bretylium

Bretylium tosylate is the prototypic adrenergic neuron-blocking drug with antiarrhythmic activity. It was first used for the treatment of hypertension and subsequently as a prophylactic antiarrhythmic agent and for the treatment of ventricular fibrillation [129,130].

Bretylium administration produces an initial sympathomimetic effect caused by norepinephrine release from adrenergic neurons followed by adrenergic blockade. Elimination is significantly reduced in renal failure [131]. Rapid

administration produces a biphasic hemodynamic response, with an initial increase followed by a subsequent decrease (within 15 to 30 minutes) in heart rate and blood pressure [132]. Patients with a fixed cardiac output from severe pump failure or aortic stenosis may be unable to compensate for the peripheral vasodilation caused by bretylium. Hypotension is postural and may be treated by placing the patient supine or in Trendelenburg's position. If this is insufficient, volume expansion or infusion of vasopressors such as dopamine or norepinephrine may be required. Patients receiving long-term bretylium infusions often demonstrate exaggerated catecholamine responsiveness [132]. After overdose, hemodynamic effects may persist for longer than 3 days.

Ibutilide and Dofetilide

Ibutilide and dofetilide, the newest class III, and first "pure" action potential–prolonging agents, are approved for termination of atrial fibrillation and flutter [133–135]. Both drugs are structurally similar to sotalol but have no beta-blockade effect. They prolong APD by a dual mode of action, initially blocking the rapid component of the delayed rectifier potassium current and enhancing the noninactivating component of the inward sodium current that flows during the plateau (phase 2) of the action potential. The net effect is to increase atrial and ventricular refractory period APD. Although very little information is available about overdose toxicity, development of torsade de pointes is the major concern. With therapeutic doses, the incidence of this arrhythmia ranged from 3.6% to 12.5% in clinical trials. Most episodes were self-limited, but some were sustained and required cardioversion. Nonsustained monomorphic ventricular tachycardia may also be provoked by ibutilide [136].

Adenosine

Adenosine is an endogenous purine nucleoside normally present in all cells in the human body. Intravenous adenosine, administered as a rapid infusion, is used for termination of supraventricular arrhythmias. An increased heart rate as compensation for peripheral vasodilation has been reported in patients with atrial fibrillation and flutter or if an atrial impulse is conducted via an accessory pathway [137–139]. Adenosine may also induce atrial fibrillation as a result of the decrease in atrial APD. It should be used with caution in patients with asthma because it can provoke bronchospasm. Short periods (longer than 6 seconds) of asystole are commonly seen after termination of supraventricular arrhythmias.

Therapeutic and toxic doses of adenosine induce intense vasodilation, flushing, and a feeling of pressure or pain in the chest that patients often describe as extremely unpleasant. The duration of these effects is extremely short (measured in seconds) with bolus therapy but can be prolonged in patients receiving continuous infusions during radionuclide studies or those patients taking dipyridamole [140].

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CHAPTER 121 ■ ANTICHOLINERGIC POISONING†

KEITH K. BURKHART

The classic anticholinergic syndrome manifests an easily recognizable toxidrome, but patients may present with some but not all of the classic symptoms. Decreased secretions, tachycardia, mydriasis, and delirium are those most commonly seen [1]. The presence of coingestants and the multiple pharmacologic actions of many anticholinergic drugs may mask anticholinergic manifestations, although anticholinergic effects often persist longer than other pharmacologic actions [2]. The anticholinergic syndrome is more accurately an antimuscarinic syndrome. However, it is conventionally called anticholinergic and is referred to as such herein.

Anticholinergic poisoning may result in seizures, delirium, and coma, along with their associated complications. Anticholinergic-induced coma and respiratory failure may require mechanical ventilation. As with any toxicologic emergency, supportive care is of paramount importance. Physostigmine is an effective antidote with proven benefits, but also has a risk for serious adverse events.

†*The views expressed in this chapter do not necessarily represent the views of the Food and Drug Administration of the United States.*

EPIDEMIOLOGY AND SOURCES

A variety of pharmaceuticals and naturally occurring products can produce an anticholinergic syndrome (Table 121.1). Many drugs with anticholinergic effects may be classified in a manner that does not identify this activity (e.g., histamine-1 [H_1]–blockers, gastrointestinal and genitourinary tract antispasmodics, cough and cold preparations, over-the-counter sleep aids, and anticholinergic plants). For some, anticholinergic effects are desirable (e.g., atropine to treat bradycardia induces mydriasis and inhibits secretions). For others, the anticholinergic effects are an undesirable side effect (e.g., antihistamines, antipsychotics, and tricyclic antidepressants).

Pharmaceuticals and plants with anticholinergic action may be intentionally abused for mind-altering effects; especially common is the use of *Datura stramonium* (jimsonweed) [3]. Anticholinergic toxicity has occurred by a number of routes other than ingestion, including inhalation of nebulized medication [4], inhalation of pyrolysis products (e.g., the smoking of plant parts) [3], transdermal use, and ocular instillation.

PHARMACOLOGY

Anticholinergic agents antagonize the effects of the endogenous neurotransmitter acetylcholine (ACh). Receptors for ACh are widely distributed in the body, including the central nervous system and the sympathetic and parasympathetic ganglia, postganglionic parasympathetic terminals, and motor end plates of the peripheral nervous system.

ACh receptors are divided into two types, muscarinic and nicotinic, based on their ability to bind muscarine or nicotine. This division has a functional significance as well, best described in the peripheral nervous system, where muscarinic receptors predominate in the parasympathetic terminals and nicotinic receptors in autonomic ganglia and motor end plates. Most drugs have predominant effects on one of the two main ACh receptors, but at high doses, there may be some crossover effect. For example, nicotine primarily stimulates nicotinic receptors. Stimulation produces tachycardia, hypertension, muscle fasciculations, and receptor fatigue, with consequent paralysis at high doses. Nicotinic antagonists, such as the nondepolarizing muscle relaxants (e.g., pancuronium), block the action of ACh at the motor end plate and produce skeletal muscle paralysis. Excessive muscarinic receptor stimulation (e.g., organophosphate poisoning) leads to the cholinergic toxidrome (see Chapters 128 and 141). Agents that block muscarinic receptors may cause anticholinergic toxicity, the focus of this chapter.

Many drugs with anticholinergic properties undergo extensive hepatic metabolism into active and inactive metabolites. A number of these drugs may have half-lives greater than 12 to 24 hours (e.g., tricyclic antidepressants). More important may be the persistence of muscarinic receptor binding. In the intensive care unit (ICU), many patients emerge from coma into a delirious state. Reversal by physostigmine suggests persistence anticholinergic delirium rather than ICU psychosis [2].

CLINICAL PRESENTATION

Anticholinergic effects have been classically described by the mnemonic "Blind as a bat, Hot as Hades, Dry as a bone, Red as a beet, and Mad as a hatter" in reference to the consequences of ciliary muscle paralysis, hyperthermia, anhydrosis, vasodilation, and delirium, respectively. The toxidrome has been subdivided into the peripheral anticholinergic syndrome and the central anticholinergic syndrome (Table 121.2). The former

TABLE 121.1

SOME AGENTS THAT CAUSE ANTICHOLINERGIC SYNDROME[a]

Pharmaceuticals	Plants
Antihistamines (H1-blockers)	*Atropa belladonna* (deadly nightshade)
Brompheniramine	*Brugmansia arborea* (angel's trumpet)
Chlorpheniramine	*Brugmansia suaveolens* (angel's trumpet)
Clemastine	*Cestrum diurnum* (day-blooming jessamine)
Cyclizine	*Cestrum nocturnum* (night-blooming jessamine)
Cyproheptadine	*Cestrum parqui* (willow-leaved jessamine)
Dimenhydrinate	*Datura metel* (downy thorn apple)
Diphenhydramine	*Datura stramonium* (jimson weed)
Hydroxyzine	*Hyoscyamus niger* (black henbane)
Meclizine	*Lycium halimifolium* (matrimony vine)
Promethazine	Mushrooms
Pyrilamine	Myristicaceae
Tripelennamine	*Myristica fragrans* (nutmeg)
Antiparkinsonian drugs	*Amanita muscaria* (fly agaric)
Benztropine	*Amanita pantherina* (panther mushroom)
Biperiden	Physalis heterophylla (ground cherry)
Ethopropazine	Solanaceae
Procyclidine	*Solanum carolinense* (wild tomato)
Trihexyphenidyl	*Solanum dulcamara* (bittersweet)
Antipsychotics[b]	*Solanum nigrum* (black nightshade)
Acetophenazine	*Solanum pseudocapsicum* (Jerusalem cherry)
Chlorpromazine	*Solanum tuberosum* (potato)
Clozapine	Verbenaceae
Fluphenazine	*Lantana camara* (wild sage)
Haloperidol	
Iloperidone	
Loxapine	
Molindone	
Olanzapine	
Paliperidone	
Perphenazine	
Prochlorperazine	
Quetiapine	
Risperidone	
Thioridazine	
Thiothixene	
Trifluoperazine	
Ziprasidone	
Antispasmodics	
Anisotropine	
Clidinium	
Dicyclomine	
Isometheptene	
Methantheline	
Propantheline	
Stramonium	
Tridihexethyl	
Belladonna alkaloids and related synthetic congeners	
Atropine (racemic hyoscyamine)	
Glycopyrrolate	
Hyoscine	
Ipratropium	
Methscopolamine	
Scopolamine	
Cyclic antidepressants	
Amitriptyline	
Amoxapine	
Desipramine	
Doxepin	
Imipramine	
Maprotiline	
Nortriptyline	
Protriptyline	
Trimipramine	
Zimelidine	
Muscle relaxants	
Cyclobenzaprine	
Orphenadrine	
Mydriatics	
Cyclopentolate	
Homatropine	
Tropicamide	

[a] Many of these agents have other significant toxic manifestations in addition to their anticholinergic effects.
[b] Some of the antipsychotics have minimal muscarinic binding.

TABLE 121.2

MANIFESTATIONS OF THE ANTICHOLINERGIC SYNDROME

Peripheral anticholinergic signs and symptoms
Cardiovascular: hypertension and tachycardia
Skin: dry and flushed with dry mucous membranes
Eyes: mydriasis (variable)
Genitourinary: urinary retention and decreased bowel sounds (ileus)
Central anticholinergic signs and symptoms
Loss of short-term memory and confusion, disorientation, psychomotor agitation
Visual/auditory hallucinations or frank psychosis
Incoordination and ataxia
Picking or grasping movements and extrapyramidal reactions
Seizures
Coma with respiratory failure

is due to quaternary amines (e.g., glycopyrrolate), which are charged molecules that poorly penetrate the blood–brain barrier, whereas the latter is due to tertiary amines (e.g., atropine), which are uncharged and reach the central nervous system. The most serious anticholinergic manifestations include agitated delirium, hyperthermia, and seizures. Patients may present with primarily peripheral signs and symptoms, primarily central ones, or both. In addition, central symptoms may persist longer than the peripheral manifestations.

The clinical presentation may be complicated by other pharmacologic actions of the intoxicant (e.g., tricyclic antidepressants) or the actions of other potentially toxic substances (e.g., salicylates, sympathomimetics).

MANAGEMENT

Traditionally, anticholinergic-poisoned patients have been managed with conservative supportive care. Obtaining and assessing historical and physical data confirms or provides the diagnoses that guide management decisions. Historical data may be simple in terms of a single agent, such as jimsonweed, or complex, as in a polydrug overdose. An analysis of the pharmacologic properties of the known intoxicants guides management decisions.

Delirium and coma are typically the most serious anticholinergic consequences that would require ICU admission. Shortly after exposure, most patients demonstrate sinus tachycardia and hypertension. These abnormalities are usually mild, but occasionally require medical intervention. Patients' respiratory status should be continuously monitored because of potential for respiratory failure. Hyperthermia, although not often present, is occasionally severe and may require rapid cooling measures. Foley catheter insertion may be needed for urinary retention.

Laboratory studies that should be considered in patients with moderate to severe anticholinergic toxicity include serum electrolytes; blood urea nitrogen; creatinine; and creatine phosphokinase, urinalysis, and electrocardiogram. Rhabdomyolysis and dehydration may be evident. A urine toxicology screen does not detect most anticholinergic agents and typically contributes little to the diagnostic workup or patient management. Many anticholinergic agents are not detected even on comprehensive toxicology screens that take hours to return [5]. Resolution of mental status changes after physostigmine administration may be the most rapid and cost-effective way to arrive at the diagnosis and simultaneously treating the poisoning.

Gastrointestinal decontamination (see Chapter 117) should be considered, especially for plant ingestions where symptoms often persist for days. Administration of activated charcoal is recommended. Its administration, however, may be problematic for the agitated or delirious patient. Physostigmine administration has also been recommended to facilitate activated charcoal administration [6].

Hallucinations, agitation, and delirium have been traditionally treated with benzodiazepines (e.g., diazepam, lorazepam) and butyrophenones (e.g., haloperidol). Heavily sedating doses may often be required such that endotracheal intubation becomes necessary, however [2]. Furthermore, haloperidol use often worsens the anticholinergic delirium, and should not be used. Physostigmine, as an antidote, reversibly binds to acetylcholinesterase and prevents this enzyme from degrading ACh, thereby allowing the neurotransmitter to persist, accumulate, and competitively reverse muscarinic receptor inhibition at its postsynaptic sites of action. Physostigmine, as opposed to similar drugs such as neostigmine and pyridostigmine, is a tertiary rather than a quaternary amine and effectively crosses the blood–brain barrier. As a result, it is effective in reversing central as well as peripheral anticholinergic effects. A more liberal use of physostigmine has the potential to help many patients and save resources. Use as a diagnostic tool may avoid an expensive workup. It may also avoid alternative treatment with other drugs and the costs of potentially having to intubate the heavily sedated patient [7,8].

Physostigmine administration allegedly has contributed to poor outcomes, especially after cyclic antidepressant poisoning [7–9]. When administered in excessive amounts or to a patient not in an anticholinergic state, signs and symptoms of cholinergic excess may appear. Several case reports [9,10] and an animal study [11] describe asystole, seizures, and death when physostigmine was used to treat tricyclic antidepressant poisoning. A recent review of reports and studies questions the justification for an absolute contraindication to physostigmine's use in all cyclic antidepressant cases [12]. A retrospective series of 39 patients treated with physostigmine included cyclic antidepressant poisoned patients [13]. None of these patients developed dysrhythmias or needed atropine, while one patient had a self-limited seizure. Reports have also described the benefits following olanzapine poisoning [7,8]. Close observation is mandatory following reversal of anticholinergic-induced respiratory or CNS depression, especially early in the course of intoxication. The awakening and cholinergic effects theoretically could enhance gut activity and further absorption of ingested drugs such that when physostigmine is cleared the patient might have greater toxicity than at the time of first administration.

Physostigmine can be both diagnostic [13] and therapeutic (Table 121.3). Administration to the confused, febrile patient may return mental status to normal and reduce fever. A head computerized axial tomogram and lumbar puncture may be avoided if the patient awakens and provides a history that is consistent with the anticholinergic toxicity. On theoretic grounds, it has been suggested that physostigmine may be useful for seizures unresponsive to conventional treatment; severe hypertension resulting in acute symptoms or end-organ dysfunction; and supraventricular tachycardias resulting in hemodynamic instability, cardiac ischemia, or other organ dysfunction. In clinical practice, these indications rarely arise and physostigmine is almost exclusively used as a diagnostic aid and for the treatment of central nervous system excitation (psychomotor agitation) and coma.

Contraindications to the use of physostigmine include bronchospasm and mechanical obstruction of the intestine

TABLE 121.3

SUMMARY TREATMENT RECOMMENDATIONS FOR ANTICHOLINERGIC TOXICITY AND USE OF PHYSOSTIGMINE

Place patient on cardiac and pulmonary monitor
Obtain electrocardiogram—If QRS prolonged more than 100–110 msec, physostigmine should not be used
Consider a urinary catheter
Consider pretreatment with 1 mg lorazepam IV
If no QRS prolongation, administer 2 mg physostigmine IV over 4 minutes
If no resolution of delirium and no bradycardia or seizures, consider repeat dosing of 1–2 mg physostigmine IV
If appropriate response, repeat 1–2 mg physostigmine as necessary

or urogenital tract. It should be used with caution in patients with asthma, gangrene, diabetes, cardiovascular disease, or any vagotonic state, and with choline esters or depolarizing neuromuscular-blocking agents (e.g., succinylcholine). Physostigmine should also be used cautiously after cyclic antidepressant overdose and is contraindicated in patients with evidence of cardiac conduction delay (e.g., atrioventricular block and prolonged QRS interval) on electrocardiogram.

Patients receiving physostigmine should be placed on continuous cardiac monitoring and be under continuous careful observation. Recommendations for the safe use of physostigmine center on its slow intravenous infusion at a rate not to exceed 0.5 mg per minute to avoid adverse drug events such as bradydysrhythmia and seizures. Slower rates of administration can be used and simply delay the onset. The average does needed for adults is approximately 2 mg [2]. Mental status improvement is usually seen within 5 to 20 minutes of administration. If no reversal of anticholinergic effect has occurred after 10 to 20 minutes, an additional 1 to 2 mg may be administered. Administration by continuous infusion has been used following the ingestion of an anticholinergic plant, *Atropa belladonna* [14]. The recommended dose in pediatric patients is 0.02 mg per kg at 0.5 mg per minute. The half-life of physostigmine is short and its duration of action after the 2-mg dose typically is only 1 to 6 hours [15]. The action of many anticholinergic agents persists longer and, therefore, additional doses may be needed [15]. In one case series of physostigmine use for anticholinergic toxicity, two-thirds of patients required just one dose of physostigmine, and no patient required another dose more than 6.5 hours after the first dose [15]. If cholinergic toxicity emerges, atropine is not needed unless severe toxicity develops. Seizures are rare and usually self-limited; diazepam is recommended as needed. Anecdotally, some physicians have administered lorazepam, 1 mg, before the physostigmine as an additional safety measure.

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CHAPTER 122 ■ ANTICONVULSANT POISONING

STEVEN B. BIRD

Anticonvulsants can be divided into four groups based on their primary mechanism of action: those that primarily act on neuronal membranes (membrane-active agents), those that act on neurotransmitters or their receptor sites (synaptic agents), those with multiple sites of action, and those that are not yet understood. Membrane-active agents alter ion fluxes and include carbamazepine (CBZ), oxcarbazepine, ethosuximide, zonisamide, phenytoin, and lamotrigine (LTG). Synaptic agents primarily affect the activity of gamma-aminobutyric acid (GABA) and include barbiturates, benzodiazepines, gabapentin (GBP), tiagabine, and vigabatrin. Agents that have multiple sites of action include valproate, GBP, felbamate, and topiramate, and those for which mechanisms of action still are not understood are levetiracetam, stiripentol, and remacemide [1–3].

(Barbiturates and benzodiazepines are discussed in Chapter 143.) The precise action mechanisms of many of the newer anticonvulsants also remain unknown. Even within groups, the site or mechanism of action may differ. Pharmacologic differences are important from a therapeutic standpoint. In the treatment of seizures, combining agents from different groups may be effective whenever a single agent is ineffective or requires a toxic dose for efficacy. Therapeutic synergism may also occur when different agents of the same group are combined (e.g., benzodiazepines and barbiturates).

PHENYTOIN

Phenytoin (diphenylhydantoin) is the most commonly used anticonvulsant medication [4]. It is also used in the treatment of trigeminal neuralgia. Phenytoin was the antidysrhythmic of choice for digitalis toxicity before the advent of digitalis Fab fragments [5]. Iatrogenic intoxications can occur with drug interactions because distribution, protein binding, and clearance of phenytoin are affected by other medications and disease states. Toxicity may occur when the daily-administered dose exceeds endogenous metabolism and elimination [6–8]. Toxicity may also result when switching dosage forms or between generic and proprietary forms of the drug because of different release and absorption characteristics. There are idiosyncratic and hypersensitivity reactions associated with therapeutic use that are unrelated to dose, most commonly seen in patients with underlying neurologic disorders [9].

Pharmacology

Phenytoin is the prototypic membrane-active anticonvulsant. It acts on sodium pumps and channels in excitable cell membranes and is classified as a type 1B antidysrhythmic agent. By blocking the accumulation of intracellular sodium during tetanic stimulation, it limits the posttetanic potentiation of synaptic transmission and prevents seizure foci from detonating adjacent areas.

Phenytoin is a weak acid, with a pK_a of 8.5. The intravenous (IV) form has a pH of 10 to 12, contains 50 mg per mL, and is dissolved in a 40% propylene glycol and 10% ethanol vehicle. The phenytoin prodrug fosphenytoin (Cerebyx) has a pH between 8.6 and 9.0 and greater solubility. It is compatible with common IV preparations, lacks the cardiotoxic diluent propylene glycol, and may be administered intramuscularly as well as intravenously. It has a conversion half-life of 8.4 to 32.7 minutes to active phenytoin and is dosed in phenytoin equivalent (PE) units (75 mg per mL of fosphenytoin equals 50 mg per mL of phenytoin) [10]. In many institutions, fosphenytoin has replaced phenytoin.

Absorption occurs in the duodenum but depends on dosage form, gastric emptying, and bowel motility. Peak levels occur between 2.6 and 8.9 hours after oral dosing of an extended-release capsule. In overdosage, absorption may continue for up to 7 days, possibly due to decreased gastric motility and pharmacobezoar formation. The volume of distribution (V_d) of phenytoin is 0.6 L per kg, and it distributes preferentially into the brainstem and cerebellum [11]. Phenytoin is highly protein bound; decreased protein binding increases the free, pharmacologically active form of the drug and the V_d. Because usually only total phenytoin levels are measured, toxicity from increased free phenytoin may occur at lower total phenytoin levels [8].

Hepatic metabolism of phenytoin follows first-order elimination kinetics, with an average half-life of 22 hours (range: 7 to 55 hours). When plasma levels exceed 10 µg per mL, metabolism follows zero-order elimination kinetics, yielding a much longer half-life. The enzyme system may be induced or inhibited by other drugs, inherited genetic disturbances, or liver disease [12,13].

The anticonvulsant effects of phenytoin occur with plasma levels between 10 and 20 µg per mL. This can be achieved within 45 to 60 minutes by an IV-loading dose of 15 to 20 mg per kg of phenytoin or PE units of fosphenytoin. The rate of IV phenytoin administration should not exceed 50 mg per minute because of propylene glycol toxicity [14]. To avoid hypotension, fosphenytoin administration should not exceed 150 PE units per minute. Phenytoin has been successfully administered by the interosseous route in children with poor venous access. Maintenance dosing is usually 4 to 6 mg per kg per day in single or divided doses, although neonates may require higher doses (5 to 8 mg per kg per day) [15]. Death from isolated phenytoin ingestions is unusual but has been reported in young children with ingestions of 100 to 220 mg per kg [16,17]. Death results from central nervous system (CNS) depression with respiratory insufficiency and hypoxia-related complications.

Clinical Manifestations

Toxicity resulting from acute and chronic intoxication has a similar presentation. Patients with serum phenytoin concentrations between 20 and 40 µg per mL typically have nausea, vomiting, normal to dilated pupils, nystagmus in all directions, blurred vision, diplopia, slurred speech, dizziness, ataxia, tremor, and lethargy [18]. They may also be excited and agitated. As phenytoin serum concentration increases, confusion, hallucinations, and apparent psychosis may develop. Progressive CNS depression occurs, and nystagmus may improve. Pupillary response becomes sluggish, and deep tendon reflexes diminish [7]. Severe toxicity with coma and respiratory depression occurs with serum concentration exceeding 90 µg per mL [19]. Slowing of alpha wave activity is seen on electroencephalograms. As toxicity increases, brainstem evoked potentials are suppressed and may be absent. Paradoxical hyperactivity has been reported in patients with underlying neurologic deficits, with findings of dystonia, dyskinesia, choreoathetoid movements, decerebrate rigidity, and increased seizure activity [7,20]. Patients with baseline focal neurologic deficits may show contralateral abnormalities, including hemianopia, hemianesthesia, and hemiparesis. Patients recover completely if no anoxic or hypoxic complications develop during acute toxicity. Cerebellar atrophy after acute intoxication with phenytoin that was not known to be attributed to hypoxia has been reported, however [21]. Recovery may take 1 week or longer.

In rare instances, chronic toxicity has been associated with a syndrome of inappropriate antidiuretic hormone [22], encephalopathy, and cerebellar degeneration [11]. Chronic use of phenytoin causes hyperglycemia, vitamin D deficiency and osteomalacia, folate depletion, megaloblastic anemia, and peripheral neuropathy. Other adverse drug events include altered collagen metabolism that causes hirsutism, gingival hyperplasia, keratoconus, and hypertrichosis [23].

Non–dose-dependent phenytoin adverse drug events include hypersensitivity reactions such as fever, rash eosinophilia, hepatitis, lymphadenopathy, myositis, a lupuslike syndrome, rhabdomyolysis, nephritis, vasculitis, and hemolytic anemia [9]. Phenytoin administration during pregnancy has resulted in fetal hydantoin syndrome [24].

Phenytoin-induced dysrhythmias, hypotension, congestive failure, respiratory arrest, and asystole result predominately from propylene glycol toxicity during rapid IV phenytoin administration (e.g., > 50 mg per minute). If the rate of infusion is slowed or temporarily halted, these effects usually resolve spontaneously but may persist for 1 to 2 hours [17,25]. Cardiovascular toxicity from phenytoin intoxication itself is rare,

represents significant toxicity, and primarily occurs in patients with underlying cardiac disorders [26,27].

Diagnostic Evaluation

Essential laboratory studies should include sequential serum phenytoin levels (free and total, if available) and levels of other anticonvulsant medications, particularly when enteric-coated dosage form is involved. The interval between drug levels should be based on factors such as severity of intoxication, rate of rise of levels, and time since exposure. Intervals should be more frequent during the initial evaluation phase, while absorption is still occurring, than later, during the postabsorptive phase. In stable patients whose drug levels have peaked or started to decline, it may be appropriate to obtain levels every 12 to 24 hours until they return to the therapeutic range. Recommended laboratory studies include serum complete blood cell count, electrolytes, blood urea nitrogen, creatinine, glucose, albumin, and liver function tests. In hypoalbuminemic patients, the corrected phenytoin concentration is equal to the measured phenytoin concentration multiplied by 4.4 and divided by the serum albumin level. In all deliberate overdoses, an electrocardiogram (ECG) and acetaminophen and salicylate levels should be obtained. Arterial blood gas, chest radiograph, head computed tomography, and lumbar puncture should be obtained as clinically indicated.

The differential diagnosis of phenytoin intoxication includes sedative–hypnotic agents, other anticonvulsants, phencyclidine, neuroleptic agents, and other CNS depressant drugs. Other conditions such as diabetic ketoacidosis; hyperosmolar nonketotic coma; sepsis; CNS infection, tumor, and trauma; seizure disorders; extrapyramidal syndromes; postictal states; and cerebellar abnormalities may also mimic phenytoin intoxication.

Management

Patients should have a rapid evaluation of respiratory status followed by intubation if hypoxia or risk of aspiration is present. Vascular access should be established and the patient placed on continuous cardiac monitoring. If the mental status is abnormal, a fingerstick blood sugar should be obtained. Patients who are hyperglycemic from phenytoin intoxication can be treated with discontinuation of the drug; insulin therapy is rarely required. Flumazenil, the benzodiazepine antagonist, has no role in managing phenytoin intoxication, even if benzodiazepines are part of the polypharmacy overdose, as its use may increase the risk of status epilepticus, particularly in patients with a preexisting seizure disorder.

Hypotension occurring during phenytoin infusion is treated with discontinuation of the infusion and administration of crystalloids. Pressors are rarely necessary. Treatment of cardiac dysrhythmias is supportive, with use of the appropriate antidysrhythmics when indicated. Type IB antidysrhythmic agents should be avoided [28].

Patients with a seizure disorder should be placed on seizure precautions due to the possibility of paradoxical seizures during the acute intoxication phase or breakthrough seizures during the recovery phase when phenytoin levels may be in the subtherapeutic range. Seizures should be treated with benzodiazepines or a different anticonvulsant.

Because phenytoin has a long elimination half-life, measures to increase the rate of elimination should be considered. Gastrointestinal (GI) tract decontamination uses oral-activated charcoal administration. Phenytoin undergoes enterohepatic recirculation with active gut secretion; multiple-dose oral activated charcoal (MDAC) can increase the rate of elimination and may decrease hospital stay [29,30] (see Chapter 117). MDAC is indicated in patients with a phenytoin concentration greater than 40 μg per mL, moderate neurologic toxicity, or rising levels after GI tract decontamination. As drug levels may continue to decline for many hours after stopping MDAC, such therapy should be discontinued before drug levels reach the therapeutic range in patients who require phenytoin for therapeutic purposes. Serum levels of concurrent anticonvulsant medications may also decline when MDAC is administered, increasing the risk of breakthrough seizures. An observation period is necessary to ensure establishment of a therapeutic anticonvulsant regimen and documentation of stable therapeutic serum levels even after passage of charcoal stools. Because phenytoin has a high degree of protein binding and hepatic elimination, forced diuresis, hemodialysis, and hemoperfusion are not useful [31]. It is anticipated that hemofiltration would not be useful for similar reasons.

Disposition

Because the majority of patients with phenytoin poisoning do well with supportive therapy alone, determining the degree of toxicity is important. After adequate GI decontamination, the patient should be assessed for progression of toxicity. Patients who are not suicidal or ataxic, have no underlying cardiac dysrhythmia, can feed themselves, and are not at risk of hurting themselves can be discharged, providing serum phenytoin levels are not rising and a reliable caretaker is available. Patients who do not meet these criteria should be admitted. Severely toxic patients, those with underlying cardiac or CNS disorder, intubated patients, or patients with rapidly progressive signs of toxicity require intensive care monitoring.

VALPROIC ACID

Valproic acid (VA) 2-propylpentanoic or 2-propyl valeric acid is structurally unique among the anticonvulsants. VA is a branched-chain carboxylic acid with a pK_a of 4.8. In addition to being an anticonvulsant medication, VA is commonly used for the treatment of acute manic episodes, mood stabilization, and prophylaxis of migraine and affective disorders.

VA is marketed as a sodium salt (Depakene); in a syrup solution; in a prodrug form, divalproex sodium (Depakote); and as a sustained-release form of divalproex sodium (Depakote ER). The latter is a molecular complex that dissociates in the GI tract into two molecules of VA. There is also a parenteral form for VA.

Pharmacology

VA is thought to mediate its anticonvulsant effect by increasing cerebral and cerebellar levels of GABA [32] by blocking its metabolism through inhibition of GABA transferase and succinic aldehyde dehydrogenase. It may also prolong the recovery of inactivated sodium channels and have effects on potassium channels in neuronal cell membranes.

VA's pharmacokinetic profile is significantly altered in an overdose setting. Within its therapeutic range (50 to 100 mg per mL), VA is 80% to 95% serum protein bound [33,34]. The degree of protein binding decreases and the V_d (0.13 to 0.22 L per kg) increases as VA levels exceed 90 μg per mL [33,34]. The resultant increase in free VA levels is evident by enhanced distribution into target organ systems and better than predicted extracorporeal drug removal. This has been demonstrated by

a higher cerebrospinal fluid-to-serum level and hemodialysis extraction ratio in the VA-poisoned patient [35,36]. Protein binding of VA may also be decreased in uremic patients or in the presence of other highly protein-bound agents (e.g., acetylsalicylic acid), which displace VA from its binding sites [37].

VA is highly bioavailable, with the time to peak serum levels after ingestion dependent on the dosage form and VA species. In capsule form, VA itself achieves peak serum levels after 1 to 4 hours in therapeutic dosing, whereas peak serum levels may be delayed 4 to 5 hours after ingestion of the enteric-coated divalproex sodium tablets. Peak serum levels may be delayed out to 17 hours in overdose [38]. This may be explained by the enteric-coating dissolution time and the sequential process of intestinal conversion of divalproex to the sodium salt. This is followed by the final conversion to the free acid, the only form absorbed from the GI tract. There is no evidence suggesting formation of pharmacobezoars from large numbers of VA tablets.

VA is metabolized predominantly by the liver, with 1% to 4% excreted unchanged in the urine [33]. It undergoes beta and omega oxidation to several metabolites: hydroxyvalproate, 2-propylglutarate, 2-propylpent-4-enoate, 5-hydroxyvalproate, and 4-hydroxyvalproate. At high doses of VA, the omega oxidation pathway may become saturated, leading to a decrease in total VA body clearance [35]. The metabolites undergo glucuronidation and biliary excretion, with a possible enterohepatic recirculation [35,39]. At therapeutic levels, VA elimination half-life averages 10.6 hours (range: 5 to 20 hours), but in an overdose it may extend to 30 hours.

VA disrupts amino acid and fatty acid metabolism, sequesters acetyl coenzyme A by forming valproyl coenzyme A, and interrupts the ornithine–citrulline shuttle and carnitine transport [40–42]. This may result in encephalopathy associated with hyperammonemia at therapeutic levels of VA [43,44], acutely contribute indirectly to the CNS-depressant effects, and chronically contribute to other target organ toxicity. VA metabolites have been implicated in the metabolic perturbations associated with VA poisoning [44,45], interfere with urine ketone determinations, and may be the hepatotoxic mediators of VA. There may be a link between VA- and opiate-induced CNS toxicity because of their similar influence on the GABAnergic systems [19,46]. Because VA and its metabolites are low molecular weight, branched chain carboxylic acids, they may be used as substrates for several enzymatic processes. This leads to inhibition of critical biochemical pathways, such as the urea cycle, and subsequent fatalities in some sensitive patient populations. Death has occurred after therapeutic doses of VA in patients with a congenital deficiency of ornithine carbamoyltransferase [47]. In addition, a frequently fatal Reye-like hepatitis has been observed in patients receiving therapeutic doses. Those at greatest risk appear to be very young patients (younger than 2 years of age), those being treated with multiple anticonvulsants, and those with other long-term neurologic complications. The fatality rate is 1 per 500 in this patient population [48]. This hepatotoxic reaction occurs in chronic exposure and may be mediated by metabolites formed via the cytochrome P450 pathway. These metabolites in turn depress fatty acid oxidation in the hepatocyte mitochondria [49]. This effect may parallel that seen after ingestion of ackee fruit containing hypoglycin, causing Jamaican vomiting sickness [49]. VA can produce a hyperammonemia and encephalopathy exclusive of the hepatotoxic reaction [39]. This may be associated with VA-induced carnitine deficiency [44].

Valproate as the sodium salt provides a significant sodium load (13.8 mg sodium per 100 mg VA) in overdose. VA and its metabolites are low-molecular-weight, osmotically active, free-acid, or anionic species. They may produce a slightly elevated osmolar gap and an elevated anion gap metabolic acidosis with a reduction in circulating endogenous cations, particularly calcium [35,40,49–53]. Valproate may have a dose-related toxic effect on bone marrow and platelet function, with resultant hematologic consequences such as thrombocytopenia, anemia, and leukopenia [54–56].

The morbidity and mortality from dose-related acute or acute-on-chronic VA poisoning appear to be related to hypoxic sequelae from respiratory failure, aspiration, or terminal cardiorespiratory arrest [35,50–52,57]. Although it has been speculated that VA has a direct, irreversible, neurotoxic effect, this has not been substantiated and it is indistinguishable from hypoxic injury [52].

Patients ingesting greater than 200 mg per kg are at high risk for significant CNS depression, but poor correlation exists between peak serum level and dose of VA ingested [57]. Patients who die from acute VA poisoning have had peak serum VA levels ranging from 106 to 2,728 µg per mL, whereas survival has been reported in a patient with a peak serum level of 2,120 µg per mL [40,49,56]. Although serum VA levels may not correlate with clinical effect, in general, serum levels of 180 µg per mL are usually associated with serious CNS toxicity (e.g., coma and apnea) and significant metabolic derangement (e.g., acidosis and hypocalcemia) [40,49,56,58,59]. The duration of toxicity is proportional to the peak serum VA level.

On the basis of endogenous VA clearance, it will take 3 days for the serum level to drop within the therapeutic range in a patient with a serum level greater than 1,000 µg per mL.

Clinical Manifestations

In acute intoxication, hypotension, mild tachycardia, decreased respiratory rate, and elevated or depressed temperature may be seen. Miosis may be present. The hallmarks of VA toxicity are global CNS-related depression in conjunction with unique metabolic changes. The mental status varies on a continuum from confusion and disorientation to obtundation and deep coma with respiratory failure. Tremor, hallucinations, and hyperactivity have been reported, but there is a notable lack of cerebellar–vestibular effects. Patients with an underlying seizure disorder may have breakthrough seizures. Most patients with serious acute VA poisoning manifest CNS toxicity for at least 24 hours and this may extend to several days. Laboratory abnormalities observed in patients with high serum VA levels include an anion gap metabolic acidosis, hypocalcemia, hyperosmolality, and hypernatremia. Transient rises in serum transaminase levels have been observed without evidence of functional liver toxicity. Hyperammonemia associated with vomiting, lethargy, and encephalopathy may occur at therapeutic serum levels. Although rare, complications or delayed sequelae associated with severe VA intoxication include optic nerve atrophy, cerebral edema, acute respiratory distress syndrome, and hemorrhagic pancreatitis.

Non–dose-related toxicity (e.g., hepatic failure, pancreatitis, red blood cell aplasia, neutropenia, and alopecia) has not been reported in acute overdoses with high serum levels of VA. Pancreatitis is usually considered a non–dose-related effect but has been observed [55]. Alopecia, thrombocytopenia, leukopenia, and anemia have been associated with acute and chronic VA intoxication.

The differential diagnosis should include opioid toxicity and a list of substances causing an increased anion gap metabolic acidosis. VA intoxication can be indistinguishable from opioid poisoning by signs and symptoms, and VA-poisoned patients may occasionally respond to naloxone. VA may cause a false-positive urine ketone determination, thereby misdirecting the clinician to causes of ketosis [40].

Diagnostic Evaluation

Essential laboratory studies should include sequential serum VA levels and levels of other anticonvulsant medications, particularly when the enteric-coated dosage form is involved. It should be recognized that VA metabolites are highly cross-reactive on enzyme-multiplied immunoassay technique assay for VA [35], and there may be an overestimation of serum VA levels as high as 50%. Recommended laboratory studies include complete blood cell count, reticulocyte count, serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, ammonia, and liver function tests. In addition, serum amylase and lipase levels should be obtained to rule out pancreatitis.

In all deliberate overdoses, an ECG and acetaminophen and salicylate levels should be obtained. Arterial blood gas, chest radiograph, head computed tomography, and lumbar puncture should be obtained as clinically indicated.

Management

As with any consequential CNS depressant ingestion, the patient's airway and respiratory status should be frequently assessed; early intubation and ventilation help prevent hypoxic sequelae. Vascular access and continuous cardiac monitoring should be established. Patients with altered mental status should have a fingerstick blood sugar determination or receive IV dextrose, followed by naloxone and thiamine as clinically indicated.

Naloxone (0.8 to 2.0 mg) has been reported to be effective in increasing the level of consciousness of patients with signs and symptoms of opioid toxicity and serum VA levels between 185 and 190 µg per mL [58,59]. Patients with higher VA serum levels have not responded to larger doses of naloxone [56,60]. Naloxone has been shown experimentally to antagonize GABA, the inhibitory neurotransmitter increased by VA [19,46]. It is therefore worth trying naloxone (up to 10 mg) all comatose patients with suspected VA poisoning. Flumazenil, the benzodiazepine antagonist, should be avoided in patients with a preexisting seizure disorder.

Carnitine has been used for the treatment of hyperammonemia because VA interferes with the citrulline–ornithine cycle and carnitine's availability to shuttle fatty acids across the mitochondrial membrane. There are some pediatric data suggesting that carnitine improves mental status [42,43,61–63]. The oral and parenteral carnitine doses range from 1.5 to 2.0 g, divided into 3 to 4 doses per day.

GI decontamination should be performed in patients with suspected VA, even if several hours have elapsed since ingestion [64]. Activated charcoal is preferred; gastric lavage and whole-bowel irrigation for enteric-coated preparations are additional options. Methods to enhance elimination may be effective since an increase in the free serum drug fraction, decreased protein binding, and marked prolongation in elimination half-life occur after overdose. MDAC may enhance the clearance and reduce the VA half-life by interrupting enterohepatic recirculation and GI tract dialysis [65]. Extracorporeal removal by hemodialysis or hemoperfusion is also effective. Indications for extracorporeal removal are not clearly defined, requiring a risk-benefit analysis on a case-by-case basis. It should be considered when the VA level exceeds 1,000 µg per mL and is recommended for patients with levels exceeding 2,000 µg per mL. In a patient with a level exceeding 2,000 µg per mL, prompt institution of hemodialysis led to complete resolution of toxicity within 3 days, whereas a similar patient managed with only supportive care died [40,56]. Patients not responding to conventional therapy or who have severe acid–base derangement may also benefit from hemodialysis. VA clearance during hemodialysis has been as high as 270 mL per minute, with a four- to fivefold decrease in elimination half-life [36]. Hemodialysis has the added benefit of correcting acid-base derangements secondary to VA and removal of its metabolites. Because of VA's extensive protein binding and predominate hepatic elimination, it is anticipated that forced diuresis, manipulation of urine pH, and hemofiltration would not be useful in the management of VA intoxication. Charcoal hemoperfusion used for VA intoxication has demonstrated clearance similar to that of hemodialysis [48,66]. Use of hemodialysis and hemoperfusion in series may be more advantageous due to a more consistent extraction of VA as its degree of protein binding increases coincident with declining levels and desaturation of binding sites [67].

Disposition

The disposition of the VA-poisoned patient is based on the severity of CNS toxicity, quantitative serum levels, evidence of hypoxic insult, risk of secondary complications, and the amount of VA ingested. Patients with serum VA levels exceeding 150 µg per mL are at risk for CNS and respiratory depression and should be observed until levels return to the therapeutic range. Patients with VA serum levels exceeding 1,000 µg per mL are at high risk for serious prolonged toxicity and should be admitted to an intensive care unit.

CARBAMAZEPINE

CBZ is an iminostilbene compound with a chemical structural backbone resembling that of the tricyclic antidepressants. It is stereochemically similar to phenytoin. CBZ has long been recognized as a well-tolerated and effective agent for the management of various types of seizure disorders. It is also used for the treatment of trigeminal and glossopharyngeal neuralgias, tabetic pain, and affective disorders [68]. A sustained-release formulation is available.

Pharmacology

Because CBZ is unionized and highly lipophilic, there is no parenteral dosage form, and the rate-limiting step for systemic absorption is tablet dissolution time [69]. Consequently, the pharmacokinetics and toxicokinetics of CBZ are not well defined and are subject to significant inter- and intrapatient variability. CBZ is 80% protein bound and may have twice the V_d of other anticonvulsants, such as phenytoin and phenobarbital.

In overdose, systemic absorption of CBZ may be inconsistent over time. This leads to intermittent surges of drug released into the circulation and may cause unexpected clinical deterioration of patients. This may explain the "cyclic coma" associated with CBZ poisoning [70–72]. Patients have been reported to relapse into deep coma as late as 2 days after admission to the hospital coincident with a marked increase in plasma levels of CBZ, even after the patient's condition has appeared to stabilize or improve clinically. CBZ's V_d ranges from 1.4 to 3.0 L per kg at toxic levels [4,73].

CBZ is predominantly metabolized in the liver, with 1% to 3% excreted unchanged in the urine. Endogenous clearance is 0.6 to 1.3 mL per minute per kg [4,68]. The variability in clearance may be attributed to alteration in the metabolic capabilities of hepatic enzymes, particularly the cytochrome P450 system [68]. This system is sensitive to autoinduction during chronic administration or, conversely, inhibition with concurrent administration of enzyme inhibitors such as erythromycin [74]. The elimination half-life of CBZ in naive users may

exceed 24 hours, whereas in chronic users it may be less than 15 hours [4,68,69,75]. Half-life determinations of CBZ, especially in overdose, often are misleading due to erratic absorption and inability to determine the contribution of sustained absorption from the GI tract [75]. Most evidence suggests that CBZ undergoes first-order kinetics, although it is postulated that some of its metabolic pathways, such as epoxidation, may follow Michaelis–Menton kinetics and saturate at high levels [75].

Forty percent of CBZ is converted to the active metabolite CBZ-10,11-epoxide (CBZ-epoxide), further complicating the kinetic and toxicity profile of CBZ [68,72]. An inactive metabolite is also formed. CBZ-epoxide elimination half-life is 5.0 to 9.8 hours and is in turn converted to the 10,11-dihydroxide [73,75]. CBZ-epoxide is much less protein bound than CBZ (50% vs. 80%) [68]. The therapeutic CBZ concentration is 3 to 14 µg per mL. Within this range, adverse drug events including nystagmus, ataxia, dizziness, and anorexia have been noted [4,76].

CBZ may be best described as a CNS depressant with mild anticholinergic activity and a proclivity for alteration of the cerebellar–vestibular brainstem function. CBZ mediates its pharmacologic effects by mechanisms that include stabilizing the inactive sodium channel, alteration of neurotransmitter activity (norepinephrine, acetylcholine), enhancement of adenosine, stimulation of benzodiazepine receptors, and depression of evoked repetitive firings in neurons and the brainstem reticular formation [68].

CBZ has been described as similar to tricyclic antidepressants in its toxicity profile [71,77–80]. Although these agents share sedative, anticholinergic, and sodium channel blocking activity, CBZ has a higher therapeutic index, and malignant cardiac dysrhythmias and seizures do not usually occur in patients with a normal cardiac and neurologic function [81]. In overdose with extremely high CBZ levels, however, fatal dysrhythmias may develop [76,82,83].

CBZ toxicity can be defined as dose dependent or non–dose dependent. Non–dose-dependent toxicity includes idiosyncratic and immunologic-mediated reactions such as bone marrow suppression, hepatitis, tubulointerstitial renal disease, cardiomyopathy, hyponatremia, and exfoliative dermatitis. It is responsible for the majority of CBZ-related fatalities [4,80,84] and is recognized in the course of chronic therapeutic dosing. Dose-related effects in sensitive populations include those with existing neurologic deficits and myocardial disease. Dose-related toxicity has been reported in acute overdoses, with survival in adults after 80-g ingestions. Death has been reported after acute ingestion of 60 g and after a 6-g ingestion in a patient receiving long-term maintenance therapy [78,85,86].

Respiratory depression and significant neurologic toxicity and death have been reported, with peak serum CBZ levels ranging from 20 to 65 µg per mL [70,72,73,76,78,79,86–92]. Patients with serum levels in the range of 10 to 20 µg per mL usually respond to verbal stimuli unless other coexisting medical complications or additional sedative–hypnotic substances are present [76].

There is poor correlation between serum CBZ levels and clinical outcome. Prognosis appears to depend on occurrence of respiratory depression and aspiration of gastric contents [71,72,76,78,79,86–89,91,93]. All reported deaths occurred in patients with a history of seizure disorders. Surviving patients may have a protracted course (days to weeks) because of secondary complications arising from hypoxic-related sequelae from respiratory and CNS depression, prolonged GI tract absorption, and a prolonged elimination half-life.

The kinetics of CBZ toxicity are affected by the active metabolite CBZ-epoxide, which may partially account for the lack of correlation between peak CBZ levels and the severity of symptoms. The concentration of CBZ-epoxide is only 40% that of CBZ. CBZ-epoxide concentration in the free, unbound form may be equal to or greater than that of CBZ, however [94,95].

Toxicity may occur by gradual accumulation of CBZ in patients receiving therapeutic dosing because of improper dosing protocols or as a result of a drug interaction with enzyme inhibitors such as erythromycin or verapamil [74] and from generic substitution [96].

Clinical Manifestations

Patients with acute and chronic exposures have similar findings. Key findings suggestive of CBZ poisoning include the triad of coma, anticholinergic syndrome, and adventitious movements [79]. Physical findings include CNS depression with pronounced effects on the cerebellar–vestibular system (e.g., nystagmus, ataxia, ophthalmoplegia, diplopia, absent doll's eye reflex, and absent caloric reflexes), central and peripheral anticholinergic toxicity (e.g., hyperthermia, sinus tachycardia, hypertension, urinary retention, mydriasis, and ileus), and neuroleptic-type movement disorders (e.g., oculogyric crisis, dystonia, opisthotonus, choreoathetosis, and ballismus), which can occur in patients without preexisting neurologic disorders.

Other effects, which are not clearly reproducible and may be indirectly related to hypoxia or occur in patients with preexisting disease, include cardiac conduction disturbances, hypotension, hypothermia, respiratory depression, deep coma, diminished or exaggerated deep tendon reflexes, and dysarthria. Some patients may be agitated and restless, combative, or irritable, experience hallucinations, or have seizures. Because CBZ has prolonged absorption from the GI tract and prolonged elimination half-life, the clinical course may be extremely protracted and deceptive, and sudden deterioration may occur days after admission [70,72].

Seizures associated with high levels of CBZ appear to occur predominantly in patients with preexisting neurologic disorders. In many reports, it is unclear whether witnessed motor activity was a true seizure or another movement disorder and whether the seizure occurred primarily or was secondary to hypoxic insult [70,71,76,77,79,88,94].

Cardiac conduction disturbances such as prolongation of the PR, QRS, and QTC intervals and complete heart block have been reported [71,88,90,97]. Patients with an underlying abnormal cardiac conduction system may be at particular risk for the development of complete heart block [98]. In most patients, conduction defects are not seen or there is marginal prolongation of intervals without progression to malignant dysrhythmia despite extremely high CBZ levels [77–79,81,90,99].

Diagnostic Evaluation

Essential laboratory studies should include sequential serum CBZ levels and levels of other anticonvulsant medications, serum electrolytes, blood urea nitrogen, creatinine, and ECG. Recommended laboratory studies include complete blood cell count and liver function tests. In all deliberate overdoses, acetaminophen and salicylate levels should be obtained. Arterial blood gas, chest radiograph, head computed tomography, and lumbar puncture should be obtained as clinically indicated.

CBZ and CBZ-epoxide are highly cross-reactive on enzyme-multiplied immunoassay technique assays for CBZ and can result in a falsely elevated CBZ level. The clinical consequence of this is debatable, however. High-pressure liquid chromatography assay has the ability to distinguish between CBZ and CBZ-epoxide. Using the ratio of CBZ to CBZ-epoxide, an index can be generated that may reflect the rapidity of absorption of CBZ from the GI tract. A ratio greater than 2.5 is evidence of

rapid or continued CBZ absorption from the GI tract. Cases in which patients appear to relapse or deteriorate may be due to an abrupt increase in absorption occurring as late as 48 hours after the initial ingestion [72,78,90,92]. In cases in which serial CBZ and CBZ-epoxide levels were monitored, the ratio greatly increased just before and coincident with the clinical deterioration [70,72,90].

Patients whose serum CBZ level continues to significantly rise, manifesting delayed symptoms, or who appear to relapse or deteriorate after appropriate GI decontamination should be suspect for harboring pharmacobezoars in their GI tract. Radiographic contrast study should be considered to confirm this diagnosis; CBZ is not radiopaque [85,99]. The differential diagnosis of CBZ toxicity includes tricyclic antidepressants, neuroleptics, sedative–hypnotics, anticholinergic agents, and other anticonvulsant poisonings.

Management

Management begins with treatment of respiratory, neurologic, and cardiovascular derangements. Early intubation and ventilation should be considered, as poor outcomes with CBZ-poisoned patients are primarily associated with pulmonary complications. Vascular access and continuous cardiac monitoring [68,70,76] should be established. Hypotension should be initially managed with crystalloid fluid challenges followed by pressor agents (e.g., dopamine) [70,78]. There is no specific antidysrhythmic regimen for CBZ-induced cardiac toxicity. IV sodium bicarbonate therapy should be considered in patients whose QRS is greater than 100 milliseconds. Patients with altered mental status should have a fingerstick blood sugar determination or receive IV dextrose, followed by naloxone and thiamine as clinically indicated. Seizures are usually self-limited but respond to IV diazepam or phenytoin [73].

GI decontamination should be initiated as soon as possible with activated charcoal. MDAC may double the elimination of systematically absorbed CBZ [100] (see Chapter 119) and should also be considered in patients with serum CBZ concentration greater than 20 µg per mL. MDAC should be discontinued before CBZ levels decline to the therapeutic range in those with an underlying seizure disorder [101]. Although MDAC therapy significantly reduces serum CBZ levels, it has not been shown to improve patient outcome [102]. In patients with rising drug levels despite initial GI tract decontamination, whole-bowel irrigation may also be useful (see Chapter 119).

Hemoperfusion has been used to enhance CBZ clearance in overdose cases but with modest results, usually no more than the increase achieved by MDAC, which is less invasive [78,87–88]. In one case, it was equivalent to an increase in CBZ excretion of 200 mg per hour [78]. If used at all, extracorporeal removal should be reserved for those with greatly elevated serum levels and concomitant deep coma. Neither urinary manipulation nor hemodialysis is useful.

Although there is one case report of a CBZ-poisoned patient (serum level: 27.8 µg per mL) who responded to a dose of flumazenil [91], this agent may precipitate seizures and is contraindicated in CBZ overdose. Physostigmine has been reported to be effective in the treatment of dystonia associated with CBZ poisoning [77]. Given that CBZ-associated dystonias are self-limited, the risks of physostigmine therapy likely outweigh its potential benefits.

Disposition

Because CBZ displays erratic absorption, the decision should be in favor of admission and a prolonged observation period in an intensive care setting for patients with a history suggestive of a large ingestion despite initial clinical presentation and CBZ serum level. CBZ-poisoned patients at greatest risk for significant sequelae should also be admitted to the intensive care unit. This would include patients whose CBZ levels exceed 20 µg per mL or are readily rising, who are obtunded or comatose, those with cardiovascular symptoms, whose ECG shows a QRS greater than 100 milliseconds, and those with seizures. The majority of patients at risk for significant sequelae require observation for a minimum of 48 hours.

NEWER ANTICONVULSANTS

Felbamate (Felbatol)

Felbamate is a phenyl dicarbamate with a structure similar to that of the sedative-hypnotic agent meprobamate. Its mechanism of action is believed to have some indirect effect on the $GABA_A$-receptor supramolecular complex [103,104], block repetitive neuronal firing, and affect the sodium channel on the neuronal membrane. Felbamate is rapidly absorbed, with a bioavailability of 90% and peak plasma concentrations occurring 1 to 4 hours after oral dosing. Its V_d is 0.75 L per kg. The drug circulates as the free drug and is only 20% to 30% protein bound. Absorption and elimination are linear and plateau at high levels. The drug undergoes partial hepatic metabolism with an inactive metabolite and renal excretion. Approximately 40% of a dose is eliminated unchanged in the urine. The elimination half-life is 20 to 23 hours. Felbamate does not induce its own metabolism [105].

Felbamate has significant drug interactions. It can inhibit and induce the P450 cytochrome system. This affects the metabolism of coadministered medications. Felbamate induces the metabolism of CBZ and inhibits the metabolism of phenytoin and VA. The effect of felbamate on metabolism takes 2 to 3 weeks to clear after discontinuation of the drug [105,106].

Although uncommon, serious adverse drug events include aplastic anemia and hepatic failure, which is associated with a 20% mortality rate. Other adverse drug events include nausea, vomiting, abdominal pains, headache, insomnia, palpitations, tachycardia, blurred vision, diplopia, tremors, and ataxia. Children are likely to demonstrate anorexia and somnolence [105].

There is limited information regarding deliberate felbamate overdose [107,108]. A 20-year-old woman developed altered mental status, massive crystalluria, and acute renal failure after an overdose of felbamate and VA. Macroscopic urinary crystals were identified by gas chromatography as containing felbamate. Crystalluria and acute renal failure resolved with hydration. A 44-year-old man who ingested an unknown amount of felbamate, haloperidol, and benztropine recovered with supportive care. Symptoms were predominately neurologic, with ataxia, nystagmus, weakness, abnormal movements, and agitation [109]. The management of felbamate overdose is supportive care. Gut decontamination with activated charcoal would appear to be reasonable. There are no data on hemodialysis, hemoperfusion, or urinary manipulation [109].

Lamotrigine (Lamictal)

LTG, or 3–5-diamino-6 (2,3-dichlorophenyl)-1,2,4-triazine, is not structurally related to other anticonvulsants. The mechanism of action of LTG is believed to involve voltage-sensitive sodium channels and stabilizes neuronal membranes. Lamotrigine has no effect on the release of GABA, acetylcholine,

norepinephrine, or dopamine. In oral dosing, LTG is rapidly absorbed, with a bioavailability of 98%. Peak plasma levels are reached 1 to 4 hours after dosing. Protein binding is 55%, and the V_d ranges from 0.9 to 1.4 L per kg. LTG is metabolized in the liver and excreted as the glucuronide metabolite. LTG does not induce its own metabolism. The elimination half-life of the parent compound is 12 to 50 hours (mean: 30 hours) [103,105].

Adverse drug events include Stevens–Johnson syndrome, toxic epidermal necrolysis, drowsiness, dizziness, headache, unsteady gait, tremor, ataxia, somnolence, diplopia, blurred vision, and nausea [105].

There is limited information regarding deliberate LTG overdose [108,110–112]. One patient presented with nystagmus and ataxia 1 hour after ingestion. The initial ECG showed a normal sinus rhythm with a QRS of 112 milliseconds, which gradually resolved over 48 hours. In another case, ataxia, rotary nystagmus, and a normal ECG were noted. A 2-year-old boy developed tremor, muscle weakness, ataxia, hypertonia, and generalized tonic–clonic seizure after ingesting 800 mg of LTG.

The management of acute LTG overdose should include GI decontamination, continuous cardiac monitoring, and supportive care. It would be prudent to closely monitor a patient with serial ECGs for 24 to 48 hours if the initial ECG shows a prolonged QRS duration (greater than 100 milliseconds). IV sodium bicarbonate therapy has not been studied but should be considered. Benzodiazepines are appropriate for the treatment of seizures. There are no data on hemodialysis or hemoperfusion.

Gabapentin (Neurontin)

GBP is an engineered molecule based on GABA and altered to increase membrane permeability and entrance through the blood–brain barrier. Chemically, GBP is GABA with a cyclohexane ring (1-[aminomethyl]-cyclohexane) [105].

Gabapentin appears to bind to a specific site in the CNS but does not affect ligand binding to $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine, and *N*-methyl-d-aspartate sites on the neuronal membrane [103,105].

GBP is 50% to 60% absorbed from the GI tract, with peak serum levels occurring 1 to 3 hours after oral administration. Its V_d is 0.8 to 1.0 L per kg. GBP is not protein bound and does not appear to be metabolized; all of a dose is excreted unchanged in the urine. The terminal elimination half-life is 5 to 7 hours. Renal elimination and half-life are proportional to renal function. The elimination rate can neither be induced, nor can the elimination half-life be altered with repetitive dosing [105,113].

Adverse drug events include CNS depression, nystagmus, blurred vision, diplopia, mood changes, headache, weight gain, seizures, fatigue, nausea, dizziness, slurred speech, and unsteady gait [106]. Lethargy, somnolence, dizziness, drowsiness, dysarthria, diplopia, sedation, ataxia, slurred speech, and GI distress have been observed after overdose [114,115]. Signs and symptoms resolved within 48 hours without specific therapy. Treatment is supportive. There are no data on binding to activated charcoal, urinary manipulation, hemodialysis, or hemoperfusion.

Oxcarbazepine (Trileptal)

Oxcarbazepine is the dihydro derivative of CBZ and can be thought of as being a prodrug, which is almost 100% biotransformed during hepatic first-pass metabolism to the active metabolite 10,11-dihydro-10-hydroxycarbamazepine. It has the same anticonvulsant effect as CBZ. The parent and the metabolite are lipophilic and pass into the CNS. Its advantages are that it has better tolerability and does not form the CBZ-epoxide. Peak serum drug levels occur 4.5 hours after an oral dose. The V_d is 49 L per kg. The elimination half-lives of oxcarbazepine and its metabolite are 1.0 to 2.5 hours and 8 to 11 hours, respectively. Adverse drug events include hyponatremia (in up to 30% of patients) headache, ataxia, dizziness, nausea, memory impairment, concentration difficulties, anorexia, and weight gain [113,116]. Evaluation and treatment considerations are the same as for CBZ. CBZ assays cannot be used to measure oxcarbazepine levels. Oxcarbazepine concentrations are not routinely available and are generally not useful in patient management [117].

Tiagabine (Gabitril)

Tiagabine is a GABA reuptake inhibitor derived from nipecotic acid to which a lipophilic moiety has been added to improve passage into the CNS. By selectively inhibiting neuronal GABA reuptake, it prolongs the action of GABA in the synapse. It is rapidly absorbed orally, with a peak level by 0.5 to 1.0 hours after ingestion. The drug is 96% protein bound and is metabolized in the liver. There is some degree of enterohepatic circulation. The elimination half-life ranges from 4 to 7 hours in patients receiving enzyme-inducing drugs [113]. Adverse drug events include CNS depression, seizures, nausea, hypertension, tachycardia, asthenia, sedation, dizziness, mild memory impairment, abdominal pain, and nausea. Treatment is supportive.

Topiramate (Topamax)

Topiramate is a sulfamate-substituted monosaccharide compound different from other anticonvulsants. Its mechanism of action may be in part due to sodium-channel blockade, enhancing the action of GABA, and diminishing kainate-induced excitatory receptor stimulation. Oral absorption is rapid, with a peak serum level at 1.8 to 4.3 hours. The plasma protein binding of topiramate is 9% to 17%, and its V_d is 0.7 L per kg. It is 70% to 97% eliminated unchanged in the urine. The elimination half-life is 18 to 24 hours.

Development of a nonanion-gap metabolic acidosis is a relative common occurrence with topiramate use, both in therapeutic dosing as well as overdose [118]. This occurs by impairing both the normal reabsorption of filtered bicarbonate by the proximal renal tubule and the excretion of hydrogen ions by the distal renal tubule. This combination of defects is termed mixed renal tubular acidosis (RTA) [119]. Treatment of the metabolic acidosis includes cessation of the topiramate and fluid resuscitation as needed. The use of parenteral sodium bicarbonate is rarely needed. Other adverse drug events include sedation, cognitive dysfunction, paresthesias, dizziness, fatigue, weight loss, diarrhea, and urolithiasis. Treatment is supportive [113].

Levetiracetam (Keppra)

Levetiracetam (Keppra) is a new anticonvulsant used to treat partial complex seizures that is also being investigated for its mood-stabilizing properties. Although its precise mechanism of action is unknown, levetiracetam does not appear to directly interact with the GABA system. There are few case reports of overdose with levetiracetam. It appears the most common adverse effects in overdose are sedation and respiratory

depression [120,121]. There are no data regarding specific antidotal therapy for levetiracetam overdose. Treatment is supportive care.

Vigabatrin (Sabril)

Vigabatrin is an engineered GABA-related anticonvulsant with limited availability in the United States. Chemically, it is gamma-vinyl-GABA. It is a stereospecific GABA transaminase inhibitor, the S(+) enantiomer being biologically active. Its peak serum level occurs 0.5 to 3.0 hours after ingestion, and its V_d is 0.8 L per kg. There is virtually no plasma protein binding of the drug, and more than 80% of the drug is eliminated unchanged. The plasma half-life ranges from 4 to 8 hours. The cerebrospinal fluid level is 0% to 15% of the serum level [114]. Adverse drug events include visual field defects [122], diplopia, drowsiness, irritability, agitation, anxiety, psychomotor effects, depression, sedation, confusion, and ataxia [113]. A patient who ingested 8 to 12 g in an overdose developed a psychotic episode lasting 36 hours [123]. Supportive care is the mainstay of management.

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CHAPTER 123 ■ ANTIDEPRESSANT POISONING

CYNTHIA K. AARON AND ABHISHEK KATIYAR

Cyclic antidepressants constitute a major component of reported drug overdoses requiring treatment in an intensive care setting [1]. These medications are freely available to patients who are at high risk for suicide or overdose. The consequences of overdose are severe and predominantly affect the central nervous system (CNS) and cardiovascular system. Treatment of overdose is directed toward limiting drug absorption and managing complications of toxicity; there is no antidote for cyclic antidepressant toxicity.

Although iminodibenzyl was synthesized in the late nineteenth century, the pharmacology of cyclic antidepressants was not detailed until the 1940s. These compounds were designed to have antihistaminic, sedative, analgesic, and antiparkinsonian properties. Imipramine, the first of the dibenzazepines, was synthesized as a phenothiazine derivative but was found to be ineffective as a neuroleptic agent. In the late 1950s, patients taking imipramine reported that the drug had mood-elevating effects. Imipramine and later congeners have since been used in the treatment of endogenous depression. Other indications for cyclic antidepressants include therapy of enuresis in children, treatment for migraine headaches, chronic pain control, smoking cessation, panic disorders, premenstrual dysphoric syndrome, and cocaine detoxification [2,3].

Classic tricyclic antidepressants have a seven-membered central ring with a terminal nitrogen containing either three constituents (tertiary amines) or two constituents (secondary amines). Tertiary amines include amitriptyline, imipramine, doxepin, trimipramine, and chlorimipramine (clomipramine). Secondary amines include desipramine, protriptyline, and nortriptyline. Included with cyclic antidepressants are two dibenzoxazepine compounds that contain the central seven-membered ring with a heterocyclic constituent: loxapine and its demethylated metabolite amoxapine.

Maprotiline, a dibenzobicyclooctadiene, mianserin, and mirtazapine (Remeron®) are tetracyclic antidepressants [4]. Mirtazapine, a derivative of mianserin, has additional α_2-antagonist activity. Bicyclic compounds include viloxazine, venlafaxine, and zimeldine.

Trazodone and nefazodone are triazolopyridine derivatives that are structurally and pharmacologically different from the other cyclic antidepressants. Atypical antidepressants include bupropion, a unicyclic phenylaminoketone [5–10], and a large group of antidepressants called *selective serotonergic reuptake inhibitors* (SSRIs). Currently available SSRIs include fluoxetine, a straight-chain phenylpropylamine; paroxetine, a phenylpiperidine derivative; sertraline; fluvoxamine; citalopram, and escitalopram.

Venlafaxine and duloxetine are considered SSNRIs, since they have norepinephrine-reuptake inhibition effects. Although not classically considered SSRI, some antidepressant agents having serotonergic activity include mirtazapine, trazodone, nefazodone, and clomipramine. Cyclic antidepressants that are not available in the United States because of side effects include mianserin (agranulocytosis), nomifensine (hepatotoxicity and hemolytic anemia), lofepramine (hepatotoxicity and hyponatremia), and zimeldine (Guillain–Barré syndrome) [11–14].

A third class of antidepressants is the monoamine oxidase inhibitors (MAOIs; e.g., moclobemide, pargyline, phenelzine, tranylcypromine, selegiline, and isocarboxazid). They are used to treat depression, panic disorders, phobias, and obsessive-compulsive behavior. A group of MAOIs that selectively inhibit the monoamine oxidase (MAO) isoenzyme type B (MAO-B) are being used as agents to treat Parkinson's disease [15].

PHARMACOLOGY

The therapeutic effects of cyclic antidepressants are relatively similar, but their pharmacology differs considerably. The cyclic antidepressants act as neurotransmitter postsynaptic receptor blockers for histamine, dopamine, acetylcholine, serotonin, and norepinephrine (NE). They inhibit the reuptake of neurotransmitter biogenic amines and have quinidine-like membrane-stabilizing effects [3,4,11,13,14,16–19] (Tables 123.1 through 123.3). These agents may induce atrioventricular blocks [20–23] and have a direct negative cardiac inotropic effect, demonstrated by a decrease in the rate of change in left ventricular pressure and an increase in left ventricular end-diastolic pressure [17,24,25]. CNS effects may be

TABLE 123.1

CYCLIC ANTIDEPRESSANT EFFECTS ON NEUROTRANSMITTERS

Antidepressant	Effect
Receptor blockade	
Acetylcholine (antimuscarinic)	Sinus tachycardia, gastrointestinal hypomotility, warm dry skin, urinary retention, mydriasis, lethargy, hallucinations, seizures, coma
Norepinephrine	Hypotension, reflex tachycardia, orthostasis, ? seizures
Histamine	Antihistamine effects, sedation, hypotension
Serotonin	Hypotension, ejaculation disturbances
Dopamine	Endocrine disturbances (galactorrhea, impotence), dystonias
Biogenic amine reuptake blockade	
Dopamine	Hypotension, psychomotor retardation, antiparkinsonian effects
Norepinephrine	Transient hyperadrenergic state (tremor, tachycardia), adrenergic depletion (hypotension, antidepressant effects), ejaculation disturbances
Serotonin	Seizures, ejaculation disturbances, antidepressant effects

TABLE 123.2

RELATIVE POTENCIES OF CYCLIC ANTIDEPRESSANTS: RECEPTOR BLOCKADE

Compound	ACh	H_1	Alpha	5-HT	DA
Tertiary amines					
Amitriptyline	4+	3+	4+	2+	1+
Imipramine	3+	2+	4+	1+	1+
Secondary amines					
Nortriptyline	3+	3+	3+	1+	1+
Desipramine	1+	2+	2+	0	0
Dibenzoxazepines					
Amoxapine	±	2+	3+	0	2+
Tetracyclics					
Maprotiline	±	3+	3+	2+	2+
Triazolopyridines					
Trazodone	0	±	3+	0	0
SSRIs					
Fluoxetine	0	0	0	1+	0
Paroxetine	0	0	0	0	1+
Sertraline	0	0	0	0	0
Atypical					
Bupropion	0	1+	0	0	
Venlafaxine	0	0	0		

ACh, acetylcholine; DA, dopamine; H_1, histamine; 5-HT, serotonin; SSRIs, selective serotonin reuptake inhibitors.

TABLE 123.3

RELATIVE POTENCIES OF CYCLIC ANTIDEPRESSANT REUPTAKE BLOCKADE

Compound	NE	5-HT	DA	ACh
Tertiary amines				
Amitriptyline	2+	1+	1+	3+
Imipramine	2+	2+	1+	3+
Secondary amines				
Nortriptyline	3+	1+	3+	3+
Desipramine	4+	±	1+	2+
Dibenzoxazepines				
Amoxapine	3+	±	3+	2+
Tetracyclics				
Maprotiline	3+	0	1+	±
Triazolopyridines				
Trazodone	0	1+	±	0
SSRIs				
Fluoxetine	±	3+	3+	0
Paroxetine	0	4+	1+	1+
Sertraline	±	3+	0	1+
Atypical				
Bupropion	0	0	2+	1+
Venlafaxine	±	3+		

ACh, acetylcholine; DA, dopamine; 5-HT, serotonin; NE, norepinephrine; SSRIs, selective serotonin reuptake inhibitors.

related to neurotransmitter and to direct membrane effects [24,26,27]. All tricyclic antidepressants increase the density of β-adrenoreceptors.

SSRIs and SSNRIs alter serotonergic neurotransmission. The International Union of Pharmacological Societies Commission on Serotonin Nomenclature has classified at least twelve 5-hydroxytryptamine (5-HT) receptors based on operational criteria (Table 123.4). SSRIs block some serotonin receptors and inhibit the reuptake of serotonin at other receptor subtypes. Buspirone, a nonbenzodiazepine sedative-hypnotic, is a 5-HT_{1A} partial agonist and is inhibitory on serotonin neuronal firing. It has anxiolytic and antidepressant activity. Excessive stimulation can lead to hypotension. Antagonists at 5-HT_{1C}, such as ritanserin, may be anxiolytic. 5-HT_{1D} receptor subtype stimulation leads to inhibition of neurotransmitter release, and its agonist is sumatriptan, an antimigraine medication. 5-HT_2 stimulation can cause vasoconstriction. 5-HT_3 antagonists have antiemetic and antipsychotic activity (ondansetron) [28]. Classic tricyclic antidepressants affect serotonin neurotransmission by enhancing the sensitivity of postsynaptic 5-HT_{1A} postsynaptic receptors. The SSRIs alter the release of serotonin presynaptically, leading to an increase in the amount of serotonin that is available for neurotransmission without changing the sensitivity of the 5-HT_{1A} postsynaptic receptors [29]. In general, the SSRIs normalize the number and function of 5-HT_{1A} and 5-HT_2 receptors [28]. As a group, the predominant difference between SSRIs is in their effect on the hepatic cytochrome P450 system and drug–drug interactions.

Venlafaxine and duloxetine are considered selective serotonergic and NE reuptake inhibitors. Blockade of NE-α_2 receptors leads to decrease in 5-HT release. Selective serotonergic and NE reuptake inhibitors induce desensitization and downregulation of 5-HT and NE receptors, leading to disinhibition of serotonergic neurons, interruption of feedback inhibition, and increased release of synaptic 5-HT.

MAOIs inhibit the activity of MAO, a flavin-containing enzyme located in the mitochondrial membranes of most tissues [30]. MAO enzymes are divided into two families: MAO-A, which uses 5-HT as its predominant substrate, and MAO-B, whose primary substrates are 2-phenylethylamine, benzylamine, phenylethanolamine, and *O*-tyramine. Monoaminergic neurons contain predominantly MAO-A; serotonergic neurons have both. MAO-A metabolizes epinephrine, NE, metanephrine, and 5-HT. Both MAO-A and MAO-B metabolize tyramine, octopamine, and tryptamine [31]. MAO regulates intraneuronal catecholamine metabolism and mediates the oxidative deamination of epinephrine, NE, dopamine, and 5-HT. MAO also regulates ingested monoamine (tyramine, ethanolamine) in the gut that would normally be absorbed into the portal circulation [20,21]. The effect of MAOs is to increase the catecholamine storage pool by preventing intraneuronal degradation of catecholamines and 5-HT. These catecholamines can be released by indirectly acting sympathomimetic agents (e.g., amphetamine, tyramine, and dopamine). MAO-A is predominantly found in the intestinal mucosa, placenta, biogenic nerve terminals, liver, and brain, whereas MAO-B is found in the brain, platelets, and liver [22]. Exogenously administered catecholamines are metabolized through catechol-*O*-methyl transferase (COMT).

MAOIs can be divided into reversible agents (moclobemide) or irreversible (selegiline, phenylzine, isocarboxazid, and tranylcypromine). They may also be selective to MAO-A (moclobemide) or MAO-B (pargyline, selegiline). The original MAOIs (e.g., phenelzine, isocarboxazid, and tranylcypromine) are nonselective irreversible MAO-A and MAO-B inhibitors., selegiline [23]. Selegiline and tranylcypromine are metabolized to desmethylselegiline, levoamphetamine, and levomethamphetamine and will give a positive amphetamine on drugs of abuse urine screening [32].

TABLE 123.4

INTERNATIONAL UNION OF PHARMACOLOGICAL SOCIETIES COMMISSION ON SEROTONIN NOMENCLATURE[a]

Receptor	Second messenger	Location	Agonist	Effect	Antagonist	Effect
5-HT_{1A}	cAMP	CNS	Buspirone	Anxiolytic	—	—
5-HT_{1B} (rodent only)	cAMP	CNS, PNS	mCPP	—	—	—
5-HT_{1C}	cAMP	CNS	—	—	Ritanserin	Anxiolytic
5-HT_{1D}	cAMP	CNS and extracerebral vascular smooth muscle	Sumatriptan, methylsergide	Antimigraine	—	—
5-HT_{1E}	cAMP	CNS	Ergotamine	—	Methylsergide	—
5-HT_{1F}	cAMP	CNS	Ergotamine	—	Methylsergide, yohimbine	—
5-HT_{2A}	IP_3DG	Vascular smooth muscle	—	Hypertension	Ketanserin, ritanserin	Hypotension
5-HT_{2B}	IP_3DG	Stomach	Tryptamine	—	—	—
5-HT_{2C}	IP_3DG	CNS, choroid plexus	mCPP (trazodone metabolite)	—	—	—
5-HT_3	Ionic channel	CNS, PNS	—	—	Ondansetron, granisetron	Antiemetic
5-HT_4	cAMP	Cardiac (nonventricular), gastrointestinal tract, bladder	Renzapride, cisapride	Gastric motility	—	—
5-HT_5–5-HT_7	cAMP	—	—	—	—	—

[a]All 5-HT receptors are G-proteins except for 5-HT_3 receptors, which are ionic channel receptors. 5-HT_1 are negatively coupled to adenylyl cyclase; 5-HT_2 are coupled to protein kinase C via phosphoinositide breakdown; 5-HT_3 are ionic channels; 5-HT_4, 5-HT_6, and 5-HT_7 are positively coupled to adenylyl cyclase.

Data from Uhl JA: Phenytoin: the drug of choice in tricyclic antidepressant overdose? *Ann Emerg Med* 10(5):270, 1981; and Kulig K, Bar-Or, Wythe E, et al: Phenytoin as treatment for tricyclic antidepressant cardiotoxicity in a canine model. *Vet Hum Toxicol* 26:41, 1984, with permission.

cAMP, 3′,5′-cyclic adenosine monophosphate; CNS, central nervous system; 5-HT, serotonin; IP_3DG, inositol triphosphodiglyceride; mCPP, *m*-chlorophenyl piperazine; PNS, peripheral nervous system.

Cyclic antidepressants are well absorbed orally in therapeutic dosing; peak serum levels occur 2 to 6 hours after ingestion [33]. In overdose [33,34], gastrointestinal (GI) absorption may be delayed secondary to anticholinergic and antihistaminic properties of these drugs. Metabolism is predominately hepatic, with a small enterohepatic circulation [35,36]. Some cyclic antidepressants have active metabolites. The volume of distribution is large, with distribution occurring within the first several hours after ingestion [36]. Elimination half-life averages 8 to 30 hours but may be prolonged in overdose [37]. Elimination is hepatic, with minimal renal involvement. Fluoxetine has an active metabolite with an elimination half-life that extends into weeks. Cyclic antidepressants are extensively bound to serum proteins, particularly α_1-acid glycoprotein (AAG), and binding appears to be pH dependent [38]. MAO inhibitors are well absorbed orally with relatively short elimination half-lives [32]. Since the irreversible agents permanently inhibit the activity of MAO, their effects can last 4 to 6 weeks.

Toxicity from cyclic antidepressants results in CNS depression, seizures, hypotension, dysrhythmias, and cardiac conduction abnormalities [38]. Hyperthermia may occur as a result of increased muscle activity, seizures, and autonomic dysfunction [39]. These toxic effects are believed to have multiple etiologies, none of which has been fully elucidated.

Patients who ingest large amounts of cyclic antidepressants frequently present with hypotension. Several mechanisms have been suggested, including direct negative inotropic effects [17,25] and dysrhythmias, with subsequent decreases in filling time and cardiac output [39–41]. Receptor blockade produces vasodilation and autonomic dysfunction. In addition, blockade of the biogenic amine pump prevents adequate uptake and release of these neurotransmitters as active substances, thereby contributing to hypotension [11,16,40].

The CNS effects in cyclic antidepressant overdose can be quite profound. Although some of the newer cyclic antidepressants are less toxic in overdose, they can cause seizures and alteration in mental status [8,42,43]. The etiology of coma, seizures, and myoclonus is multifactorial and involves receptor blockade and direct membrane effects which all contribute to CNS derangements [42–45]. Cyclic antidepressants interact with both the $GABA_A$ and $GABA_B$-chloride ion channel in the CNS and may alter chloride flow across the receptor [46–48].

Dysrhythmias and conduction abnormalities often provide a clue to the recognition of cyclic antidepressant overdose. Action potential propagation, particularly in ventricular myocardial cells and the conduction system, is significantly affected by these drugs [49]. Cyclic antidepressants blunt phase 0 of the action potential depolarization by blocking the fast inward flux of sodium through the sodium channel [50]. This, in turn, slows the rate of rise of phase 0 (V_{max}) and slows overall action potential depolarization. As ventricular conduction slows, the QRS complex widens [50–52]. This also contributes to unidirectional blocks and reentrant dysrhythmias [52]. Because inward sodium flux is coupled to the calcium excitation in myocardial cells, the myocardial cells are unable to contract fully and become less efficient. A less toxic effect is seen on phase 4 of the action potential (spontaneous diastolic depolarization), leading to decreased automaticity [49]. Delayed repolarization occurs and may contribute to QTc interval prolongation,

which has been associated with torsades de pointes [53–56]. Because cyclic antidepressants have their tightest myocardial binding during diastole, toxicity appears to be directly related to heart rate; in amitriptyline-poisoned dogs, increasing heart rate caused a decrease in V_{max} and widened the QRS complex [50–52,57,58]. Interventions that slowed the heart rate, such as beta-blockers, improved conduction but led to irreversible hypotension [53,57].

The decrease in V_{max} during phase 0 appears to be pH sensitive [51,53,58]. Alkalinization with molar sodium lactate, sodium bicarbonate, or hyperventilation, or increasing extracellular sodium concentration, produces an increase in the rate of rise of the action potential (V_{max}), narrows the QRS complex, decreases the incidence of ventricular tachycardia, and improves blood pressure [53,58–65]. These studies also show that decreasing pH worsens conduction abnormalities, produces hypotension, and increases the incidence of dysrhythmias. A combination of increased extracellular sodium and alkalosis (or hyperventilation plus sodium bicarbonate) in vitro has been shown to be equally and possibly more effective than either alone [52,58]. The use of lidocaine in animal studies decreased automaticity and ectopy and improved conduction. However, it did not have the same salutary effect on the blood pressure as alkalinization and may have worsened inotropy [58]. Although binding of cyclic antidepressants to AAG is increased at an alkalotic pH, infusion of AAG in animals to increase serum protein binding has not been shown to be beneficial [38].

SSRI toxicity results from exaggeration of its pharmacologic activity and is manifest as the serotonin syndrome. The pathophysiology is not fully understood but is believed to result from excessive 5-HT_{1A} stimulation, although dopamine and other neurotransmitters may be involved. The serotonin syndrome is associated with SSRI use alone, change in dose, overdose, or in combination with other agents [e.g., serotonin precursor or agonists, lithium, tricyclic antidepressants, 5-HT analogs, other SSRIs, meperidine, pentazocine, tramadol, cocaine, 3,4-methylenedioxy-*N*-methylamphetamine (Ecstasy), MAOIs, and herbal remedies such as St. John's Wart].

Two forms of toxicity are caused by MAOI: acute overdose and drug and food interactions. Toxicity from acute MAOI overdose results from the exaggerated pharmacologic effects of MAOI and may be associated with secondary complications [66]. The primary drug-drug interaction occurs when MAOI is taken with an indirectly acting sympathomimetic agent (e.g., ephedrine, phenylephrine, phenylpropanolamine, and amphetamine), which causes an NE surge in the peripheral sympathetic nerve terminals. MAOI and food interaction primarily involve the small amounts of tyramine or tryptophan that are normally present in certain foods (e.g., aged cheeses, smoked or pickled meats, yeast and meat extracts, red wines, Italian broad beans, pasteurized light and pale beers, and ripe avocados) and are often termed the *cheese reaction*. These indirectly acting agents are usually metabolized by MAO-A in the gut. When MAO-A is inhibited, tyramine absorption is unregulated, enters into the portal circulation, and causes release of stored catecholamines with resultant hypertensive response [67,68].

CLINICAL TOXICITY

The onset of symptoms from cyclic antidepressant overdose is rapid. Most patients who die from overdose do so before arriving at the hospital and after having ingested large (> 1 g) amounts of drug [66]. Signs and symptoms usually occur within the first 6 hours after ingestion. Patients who survive the first 24 hours without hypoxic insult generally do well [66]. The progression of toxicity is rapid and unpredictable, with patients capable of deteriorating from an awake, alert state to seizures, hypotension, and dysrhythmias within 30 to 60 minutes and with minimal warning signs [6,69–75]. Cardiac arrest due to cyclic antidepressant poisoning may sometimes respond to prolonged resuscitative efforts. One case reports a patient who survived after a resuscitation of approximately 70 minutes [76].

Vital signs on presentation usually include tachycardia, although patients taking beta-blockers or those with underlying conduction blocks, or those in a premorbid state may present with bradycardia. Cyclic antidepressants without major antimuscarinic effects, such as trazodone, nefazodone, and the SSRIs, may not cause significant tachycardia. Bupropion-toxic patients almost always have vital signs reflecting a hyperadrenergic state [77–79]. Initial blood pressure may be elevated but can rapidly change to hypotension. The respiratory rate and body temperature may be elevated. If marked myoclonus or seizures develop, severe hyperthermia may result [39,43,71]. Cyclic antidepressants with prominent antimuscarinic effects may cause mydriasis, urinary retention, ileus, and cutaneous vasodilation (Table 123.2). Absence of these signs does not rule out cyclic antidepressant ingestion.

Dependent on the ingested agent, progression of toxicity may be precipitous and lead to coma, hypotension, seizures, dysrhythmia, and death. The newer agents (e.g., nefazodone, trazodone, the SSRIs) are more likely to be sedating and less likely to exhibit cardiovascular toxicity [69,70,73–75]. Maprotiline, venlafaxine, amoxapine, and loxapine tend to cause CNS toxicity before cardiovascular toxicity [71,80–92]. Bupropion may cause seizures in therapeutic dosing and exhibits a dose-dependent increase in toxicity (greater than 450 mg) [77,93,94]. With the cyclic antidepressants, it is unusual for patients to have significant cardiovascular disturbances without an altered mental status [10].

Cyclic antidepressant-induced seizures are generally single or brief flurries of motor activity. However, status epilepticus may occur without any prodrome, and this is especially true with amoxapine, loxapine, or bupropion. Status epilepticus may be difficult to treat; if prolonged, it leads to overall deterioration in the patient's condition, particularly with cyclic agents [25,77,93–102].

Signs of cardiovascular toxicity may exist even with therapeutic dosing of classic cyclic antidepressants. A prolonged QTc interval and sinus tachycardia may be observed on the electrocardiogram (ECG) in non-overdose states [103]. Sinus tachycardia is frequently the presenting dysrhythmia; aberrancy and ventricular tachycardia develop with increasing toxicity. As cardiovascular toxicity progresses, the frontal plane axis shifts rightward. This is gradually followed by repolarization abnormalities, intraventricular conduction delays, ventricular dysrhythmia, high-grade atrioventricular blocks, profound bradycardias, and asystole [40,104–108]. Trazodone, citalopram, and escitalopram may cause marked QTc interval prolongation and torsades de pointes (polymorphous) ventricular tachycardia in the absence of other ECG abnormalities [109].

Many of the cyclic antidepressants show early changes to the ECG axis. The terminal 40 milliseconds of the frontal plane QRS complex shifts to a rightward vector of 130 to 270 degrees. If computerized vector analysis is not available, a widened slurred S wave in leads I and aVL and an R wave in aVR represent this vector. Looking for these changes in overdosed or comatose patients may help in establishing a diagnosis. However, a small portion of the population normally has this unusual vector. Patients with extreme leftward axis deviation as a baseline may not show the rightward change with cyclic antidepressant toxicity [70,74,99,110–113]. The absence of this finding does not rule out a classic cyclic antidepressant poisoning; its presence with coma, seizures,

dysrhythmias, or hypotension is very suggestive of cyclic antidepressant toxicity [69].

The serotonin syndrome varies from mild to life threatening. Classic manifestations are altered mental status, autonomic dysfunction, and neuromuscular irritability. Signs and symptoms include tachycardia, unstable blood pressure, hyperthermia, mydriasis, diaphoresis, blurred vision, nausea, vomiting, diarrhea, shivering, tremor, incoordination, hyperreflexia, myoclonus, rigidity, agitation, confusion, delirium, seizure, and coma. Lactic acidosis, rhabdomyolysis, myoglobinuria, and multiorgan failure may develop in severe cases [101,114,115].

SSRIs, except for venlafaxine, citalopram, and escitalopram [101,109], are expected to have minimal cardiac effects. Citalopram, escitalopram, and ritanserin may significantly affect the QTc with at least one case of arrhythmia reported from citalopram [109]. Overdoses with extremely large amounts of fluoxetine and citalopram have caused atrial fibrillation and bradycardias. Evidence of Na^+ and Ca^{2+} channel blockade has been shown at extremely high serum levels [89]. Animal experiments with paroxetine required much larger doses, compared to amitriptyline, to induce dysrhythmias [6,7,82–89,91].

The onset of MAOI and food or drug interaction usually occurs within 30 to 60 minutes of ingesting the offending substance. Signs and symptoms of this type of reaction include hypertension, tachycardia or reflex bradycardia, severe (occipital) headache, nausea and vomiting, hyperthermia, altered mental status, seizures, intracranial hemorrhage, and death.

Patients with acute MAOI overdoses may be asymptomatic on presentation. Signs and symptoms typically develop within 6 to 12 hours of ingestion if the person is on the medication chronically but may be delayed for 24 hours if this is a new medication for the patient. An initial stage of neuromuscular excitation such as agitation, tremors, myoclonus, and hyperreflexia with hypertension usually occurs. The face may be flushed. As toxicity progresses, the mental status deteriorates, and there is a general elevation of all vital signs. Seizures may develop. As monoamine neurotransmitters become depleted, hypotension and cardiovascular collapse may ensue. Respiratory depression may occur and the mental status will deteriorate. If the patient survives this progression, there may be secondary complications from rhabdomyolysis, electrolyte abnormalities, lactic acidosis, and multiple organ system failure. Toxicity may last for up to 72 hours [66]. MAOI ingestions can be very challenging to manage as the patient can variably show either a hyperadrenergic state or a catecholamine depleted state. The swings in the vital signs can be rapid, unexpected, and uncontrolled [116–118].

Secondary complications, such as noncardiogenic pulmonary edema, aspiration pneumonia, and rhabdomyolysis, frequently develop in patients with antidepressant overdoses. Overdoses with agents that have prominent antimuscarinic properties (e.g., amitriptyline) may cause urinary retention, ileus, and abdominal distention. Although rare, tardive dyskinesia, neuroleptic malignant syndrome, and the syndrome of inappropriate antidiuretic hormone secretion all have been reported in association with cyclic antidepressant overdose [39,119–122]. In addition to causing seizures and cardiovascular toxicity, venlafaxine may cause direct muscle toxicity leading to severe rhabdomyolysis [123].

In therapeutic doses, cyclic antidepressant agents and SSRIs may interact with other medications, increasing the effect of one or both agents. This effect may be magnified after an overdose. Drug interactions may alter metabolism, elimination, or the free fraction of the drug. Most antidepressants are metabolized through the CYP 2D6 microsomal agents and as such, are subject to induction and interference. Agents that stimulate the hepatic P450 microsomal system (phenobarbital, carbamazepine, phenytoin, and rifampin, and cigarette smoking) increase the clearance of cyclic antidepressants. Cimetidine, as a competitor for the hepatic microsomal enzymes, leads to an increase in cyclic antidepressant levels. The coadministration of cyclic antidepressants and antipsychotic agents may lead to competitive inhibition of the metabolism of both drugs. Other medications that increase the steady-state levels of cyclic antidepressants include chloramphenicol and disulfiram, whereas erythromycin decreases the level. Acute ethanol intoxication may decrease cyclic antidepressant metabolism, resulting in markedly prolonged serum drug half-life [106].

Patients taking MAOIs should avoid any agents that have serotonergic effects or act as indirect sympathomimetics (e.g., amphetamine, ephedrine, dopamine, phenylpropanolamine, meperidine, tramadol, dextromethorphan, and St. John's wort) [124–126]. Similar effects have been reported with paroxetine with the use of phenobarbital, cimetidine, and phenytoin. The potential exists for the potentiation of warfarin effect when they are administered in conjunction with paroxetine. The interaction of fluoxetine and cyclic antidepressants causes an increase in serum levels of the cyclic antidepressant and can lead to cyclic antidepressant toxicity. Therapeutic administration of an SSRI and a cyclic antidepressant with strong serotonergic effects (e.g., clomipramine) or two SSRIs may induce the serotonergic syndrome. The interaction of MAOIs and cyclic antidepressants may lead to significant and life-threatening toxicity, particularly with those antidepressants that have predominantly serotonergic effect (trazodone, clomipramine, and the SSRIs) [29]. The administration of the selective MAO-B inhibitor selegiline with an SSRI or a cyclic antidepressants does not appear to have as strong a serotonergic effect but still may cause drug interactions [127].

Although the differential diagnosis includes many substances that share some of the effects of cyclic antidepressants, duplicating the entire constellation of signs and symptoms is relatively unusual. Like cyclic antidepressants, anticholinergic and antihistaminic medications can cause dilated pupils, GI hypomotility, confusion, and seizures. Phenothiazines also cause these effects and may increase the QTc. Thioridazine and mesoridazine, two phenothiazines, prolong the QRS and QTc. The atypical neuroleptics (risperidone and olanzapine) have similar sedative, cardiac, and movement effects. Other drugs that affect QRS width include type IA antiarrhythmics (quinidine, procainamide, and disopyramide) and type IC antiarrhythmics (flecainide, encainide, and propafenone). Hyperkalemia and hypocalcemia also widen the QRS complex, and the latter can cause muscle twitching and myoclonus. Beta-blockers, particularly propranolol, cause seizures and conduction abnormalities in overdose. Tramadol, an opiate analgesic that also causes biogenic amine reuptake inhibition, may cause opioid and serotonergic toxicity, especially when given in conjunction with an SSRI or MAOI. Cyclobenzaprine, a muscle relaxant, and carbamazepine share the cyclic antidepressant structure and can cause a similar picture with sedation, hypotension, and prolonged QTc interval.

DIAGNOSTIC EVALUATION

Patients with suspected cyclic antidepressant overdose should have routine blood analyses. Stress leukocytosis may occur with any antidepressant overdoses, especially if seizures have occurred. Electrolyte, blood urea nitrogen, creatinine, and glucose levels should be determined, with special attention to the anion gap. Because rhabdomyolysis may occur, most frequently with seizures, creatinine kinase should be followed [39,119]. Urinalysis is also useful in the diagnosis of rhabdomyolysis and possible myoglobinuric renal failure. Frequent ECGs are a necessity and should be done any time that the patient has a change in status. Arterial blood gas and chest radiograph should be obtained as clinically indicated. Since repetitive arterial sampling may be extremely painful and is sometimes

TABLE 123.5

DRUGS THAT MAY INTERFERE WITH THE TRICYCLIC ANTIDEPRESSANT QUALITATIVE DRUG SCREEN

Drugs	Minimal serum concentration level
Carbamazepine	Therapeutic range
Chlorpromazine	Therapeutic range
Cyclobenzaprine	10 to 20 µg/L
Cyproheptadine	390 to 400 µg/L
Diphenhydramine	>120 µg/L
Quetiapine	Therapeutic range
Thioridazine	Therapeutic range

associated to complications such as infection, injury, and thrombosis [128], and since venous pH has shown to strongly correlate that of an arterial sample in cyclic antidepressant overdose [128], using venous blood for the serial measurement of serum pH is recommended.

Quantitative tricyclic antidepressant levels rarely if ever contribute to the clinical patient management. Although total tricyclic levels of more than 1,000 ng per mL have been associated with significant toxicity [33,36,69,105,108], there is poor correlation between toxicity and serum level. Repeated levels during resolution of toxicity may be misleading; physical signs of toxicity abate before a significant drop in serum levels because of the prolonged elimination half-life and extensive protein binding [36]. A qualitative screen using a tricyclic antidepressant immunoassay is usually sufficient. However, other drugs that have structural similarity can produce a false-positive result (Table 123.5) [129–135] and if clinical findings are inconsistent with immunoassay results, it may be necessary to perform a more specific test such as gas chromatography with mass spectrometry. Although a toxicology testing is discretionary, acetaminophen and salicylate levels and a pregnancy test in a woman of childbearing age should always be checked.

MANAGEMENT

Patients who have ingested cyclic antidepressants require immediate evaluation and stabilization. Those who are awake and alert should receive an oral dose of activated charcoal. Patients who have ingested a classic agent (amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, dothiepin, protriptyline, and maprotiline) can be safely observed in the emergency department if they are asymptomatic. An asymptomatic patient implies one with a normal ECG throughout the observation period, a mild sinus tachycardia that resolves within the first 1 to 2 hours, clear mental status, and a nontoxic acetaminophen level. This observation period is defined as a 6-hour interval during which the patient is on continuous ECG monitoring and has intravenous access in place [49,105,119,120,136,137,139,141]. In addition, these patients must have had adequate GI decontamination and, preferably, have passed a charcoal stool. Patients should always be referred for psychiatric evaluation and pregnant women should be directed to prenatal counseling.

No consensus has been reached on emergency department observation for patients with ingestions of bupropion, trazodone, nefazodone, venlafaxine, and the SSRIs because of the paucity of overdose data for these medications [80,82,141,142]. Observation of asymptomatic patients for 6 to 8 hours or until the ECG returns to normal or baseline is reasonable. Any patient with signs or symptoms of toxicity should be admitted to the intensive care unit. Admission (or prolonged observation) is also prudent for patients with sustained-release bupropion overdose, as seizures have been reported as far as 12 to 16 hours after ingestion [141].

Symptomatic patients should have a rapid evaluation of the airway and, if obtunded or hypoventilating, be immediately intubated. Because cyclic antidepressant toxicity increases with acidemia, an ABG demonstrating a pH <7.4 or hypercarbia should prompt intubation and hyperventilation even in the patient who is able to protect his or her airway. Once an airway is established, the patient should be appropriately ventilated to prevent respiratory acidosis and subsequent deterioration of his or her condition. If the patient has an altered mental status, a rapid bedside determination of serum glucose or administration of 25 to 50 g dextrose (0.5 to 1.0 g per kg), 2 mg naloxone, and 100 mg thiamine should be given intravenously [34].

GI decontamination for severely ill patients should consist of activated charcoal with or without gastric lavage. Because some cyclic antidepressants have a small enterohepatic circulation, an additional one to two doses of aqueous charcoal (25 g) may be considered [36,138–140]. This dose should not be administered in the presence of an ileus or gastric distention. Because the majority of these agents are extensively protein bound, hemodialysis and hemoperfusion are not effective in reducing the toxic effects of cyclic antidepressants [143–146].

Single or brief flurries of seizures should be treated with a benzodiazepine [26,45,143]. Seizures are frequently isolated, and the additional use of an anticonvulsant is not indicated in this situation. Status epilepticus should be aggressively managed to prevent the development of acidosis, hyperthermia, and rhabdomyolysis [26]. As cardiotoxicity worsens dramatically in the presence of acidemia, rapid control of seizures is mandatory. Status epilepticus should be managed with large doses of benzodiazepines [143]. Failing this, management becomes controversial. Administering a nondepolarizing short-acting neuromuscular blocking agent such as vecuronium along with a barbiturate anticonvulsant (e.g., phenobarbital, 15 to 20 mg per kg, or thiopental, 3 to 5 mg per kg) is one option [146,148]. Chemical paralysis helps treat or prevent hyperthermia, rhabdomyolysis, acidosis, and further deterioration. If available, continuous electroencephalographic monitoring should be used. If the patient continues to have seizure activity once the paralytic has worn off, an additional dose of vecuronium should be given and an alternative anticonvulsant or general anesthesia should be administered [26,81,146–149]. Propofol may be useful since it has both GABA and NMDA activity but there are no data on its use in this setting. Serum alkalinization does not affect seizure activity [146].

Hypotension often responds to fluid resuscitation. Because concomitant acidosis or abnormal cardiac conduction is often present, a sodium bicarbonate solution can be used for both fluid resuscitation and serum alkalinization. A solution of 1,000 mL dextrose 5% in water with 150 mEq $NaHCO_3$ (roughly equivalent to 0.9% NaCl) is suggested. The rate of fluid administration should be adjusted to maintain a serum pH of 7.45 to 7.55 without causing hypernatremia. In an adult, an initial rate of approximately 200 to 300 mL per hour (1.5 to 2.0 times maintenance fluids) is usually adequate. Many clinicians give boluses of sodium bicarbonate (44 to 50 mEq per bolus) to achieve the same effect.

In the event of refractory hypotension, invasive monitoring (arterial line, central venous pressure, or Swan–Ganz catheterization) may be necessary. Pressor therapy with direct-acting sympathomimetics, such as NE (Levophed™), phenylephrine (Neo-Synephrine™), or epinephrine, has been shown to be more effective than indirect-acting agents, such as dopamine [26,142,150,151]. In experimental rat models, the combination of epinephrine and sodium bicarbonate increased survival and decreased the frequency of arrhythmias [142]. Moreover, this duo drug regimen was found to be more efficacious than the

combination of sodium bicarbonate and norepinephrine [152]. If hypotension remains refractory, an inotropic agent such as dobutamine may be required [142,150,151]. If the patient still persists with severe hypotension, then the use of vasopressin in addition to the use of fluids, bicarbonate, and vasopressors may be warranted. Vasopressin has been shown to sustain blood pressure and improve organ perfusion in several critical care settings, including once case study that showed immediate success in a patient who overdosed on amitriptyline [152,153]. Unlike other conventional treatments that are dependent on the catecholamine receptors, vasopressin works directly on the smooth muscle causing an influx of calcium into the cell, resulting in vasoconstriction [154]. This mechanism is mediated via the G-receptor protein, called V1. The dose required to see significant improvement is still unclear, but most authors suggest dose < 0.4 U per minute to minimize the possible adverse effects such as end organ vasoconstriction and platelet aggregation [155].

Abnormal conduction (QRS complex > 100 milliseconds in the limb leads) and ventricular dysrhythmias are treated with alkalinization. A combination of sodium bicarbonate infusion and hyperventilation may be more useful than either alone, although hyperventilation is effective if the patient cannot tolerate the sodium load [51,58,60,62,150]. By combining the two modalities, the arterial partial pressure of carbon dioxide can be maintained at approximately 30 to 35 mm Hg, which prevents cerebral vasoconstriction, while serum sodium is kept within reasonable limits. Optimal arterial pH is between 7.45 and 7.55. Ventricular dysrhythmias that are not responsive to alkalinization may respond to lidocaine or hypertonic saline. Other than β-adrenergic blockers, no antidysrhythmics have been studied; although phenytoin has been used anecdotally (see the Controversies section). In animal studies, propranolol was effective in improving conduction but led to intractable hypotension [51,58,59]. Other type IA and IC antidysrhythmics are contraindicated because they worsen cardiotoxicity. Amiodarone, a class III antidysrhythmic, was found to be of no benefit in TCA-poisoned animal models. In addition, it was felt that the use of amiodarone may have been detrimental because it can further prolong the QTc interval and cause negative inotropy [156]. The successful use of magnesium sulfate was reported in a 23-month-old child who presented with ventricular tachycardia after ingesting unknown amounts of amitriptyline. The child had received normal saline, lidocaine, bicarbonate infusion, and cardioversion without effect. Subsequent magnesium sulfate resulted in normalization of the cardiac rhythm and clinical improvement [76]. Overdrive pacing is another option, but controlled studies are lacking [54].

More recently, the use of intralipids in the clinical scenario of lipid-soluble drug toxicity such as local anesthetics and calcium channel blockers, have been gaining wide acceptance in the practice of critical care and emergency medicine [144,157–160]). Numerous studies have demonstrated significant cardiovascular improvement with severe lipid-soluble drug toxicity when infused with lipid emulsions. Most cyclic antidepressants are lipid soluble and produce significant cardiovascular instability and collapse that may be refractory to standard measures and sodium bicarbonate therapy. In animal models, infusion with intralipids proved to be more potent in reversing cardiac arrest and hypotension and also preventing further cardiovascular collapse [144,157]. Currently, there are two theories that explain why lipid emulsions may be effective. The first theory is based on the fact that the intralipids create a lipid basin that sequesters lipid-soluble drugs away from their site of action. The second theory is that lipid emulsions provide relief to a stressed myocardium by providing high energy to the heart [157,158]. This concept is similar to the use of high-dose insulin regimen for calcium channel blockers toxicity. In conclusion, intralipid infusion should be strongly considered when conventional treatments such as oxygen therapy, fluids, vasopressors, and sodium bicarbonate have failed to provide significant results.

Treatment of the serotonin syndrome is primarily supportive. Sedation, paralysis, intubation and ventilation, anticonvulsants, antihypertensives, and aggressive rapid cooling may all be necessary. Some success has been achieved with the nonspecific serotonin antagonist cyproheptadine (4 to 12 mg every 8 hours orally or 4 mg per hour) [114,115]. Dopamine-2-receptor antagonists, such as haloperidol, have occasionally been effective, but safety and efficacy data are lacking. Bromocriptine increases brain serotonin levels and is contraindicated, and dantrolene may enhance brain 5-HT metabolism and should not be used.

Any patient with an acute MAOI overdose or persistent signs and symptoms from food or drug interactions should be admitted to an intensive care setting for at least 24 hours. Therapy for food or drug interactions is aimed at lowering the blood pressure. A rapidly direct-acting agent that is easy to titrate is recommended (e.g., nitroprusside or nitroglycerine).

Treatment of MAOI overdose is entirely supportive. Muscular hyperactivity and seizures are treated with high-dose benzodiazepines. Hyperthermia that does not respond to benzodiazepine therapy and cooling requires rapid-sequence intubation and paralysis with a nondepolarizing agent to completely shut down muscle activity. Bromocriptine should not be used, as it has drug interactions and is an uncontrolled D_2 agonist and stimulant. Dantrolene is ineffective as it works peripherally and does not affect the central causes of hyperthermia [66,161–163]. Symptomatic or severe cardiovascular (sympathetic) hyperactivity should be treated with agents that have readily reversible effects and can be titrated to response. Agents such as nitroprusside, nitroglycerine, and esmolol are recommended. Nicardipine can also be used. For cardiovascular depression, direct-acting agents, such as epinephrine, norepinephrine, and isoproterenol, are preferred. Although MAO inhibition may prolong their effects, these agents are also metabolized by catechol-*O*-methyltransferase.

With the exception of MAOI overdosed patients, those who survive the first 24 hours without major complications (hypoxia, prolonged seizures, profound acidosis, and hyperthermia) generally do well. Most patients show some improvement within 24 hours. Once cardiac conduction improves (narrowing of QRS complex to 100 milliseconds), alkalinization can be discontinued (usually within 12 hours) and the pH allowed to normalize. If the QRS complex again widens, alkalinization should be resumed and the weaning process repeated. Once the ECG has normalized without alkalinization, the patient should be monitored for an additional 12 to 24 hours in the intensive care unit. The patient should be awake and alert and have passed a charcoal stool before transfer out of the unit. All overdose patients should be referred for psychiatric evaluation before discharge [6,104–106].

OTHER MANAGEMENT CONSIDERATIONS

Controversial or investigational therapies for cyclic antidepressant poisoning include phenytoin, physostigmine, prophylactic alkalinization, mechanical cardiovascular support, antibody therapy, and adenosine antagonists. Although phenytoin binds to voltage-dependent Na^+ channels and prevents propagation of seizures, it has no GABA effect and does not prevent toxic seizures. Some animal studies suggested that phenytoin was effective but others did not [151,164]. Studies using phenytoin to improve cardiac conduction were poorly controlled and not reproducible [105,147,164–166]. Canine data showed that

phenytoin transiently facilitates conduction but then increases the incidence and duration of ventricular tachycardia and does not improve survival, suggesting that phenytoin is potentially detrimental [164].

Physostigmine (see Chapter 121) has been used to antagonize the antimuscarinic effects of cyclic antidepressants such as agitated delirium [147,167–169]. However, bradycardia and asystole have been reported with physostigmine in the presence of aberrant conduction, and as a carbamate, it may precipitate seizures [65]. Thus, physostigmine is not advocated to treat acute cyclic antidepressant overdose [169] and is contraindicated in those with cardiac conduction disturbances.

No studies have been done regarding prophylactic alkalinization in patients with normal cardiac condition. Because altering the pH alters the reliability of the QRS width as a predictor of cardiotoxicity, such therapy is not recommended. Alkalinization is also not without risks, including hyperosmolality, cerebral vasoconstriction, and alterations in ionized calcium concentrations. There is no evidence that it affects the seizure threshold.

In moribund patients in whom conventional therapy has failed, the use of mechanical circulatory support, such as intraaortic balloon pump assist or partial cardiac bypass, may be life-saving. In this situation, the use of extracorporeal measures supports myocardial, hepatic, and cerebral perfusion while allowing the liver endogenously to detoxify the cyclic antidepressant [170].

Adenosine receptors may be involved in cyclic antidepressant-induced cardiovascular toxicity. Adenosine receptor activation has been shown to cause peripheral vasodilation, decrease in cardiac output, and degranulation of mast cells [171]. In animals with cyclic antidepressant poisoning, adenosine receptor antagonists have reversed hypotension and QRS prolongation [171].

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CHAPTER 124 ■ ANTIPSYCHOTIC POISONING

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Antipsychotic agents, sometimes termed *neuroleptics* and *major tranquilizers*, are primarily used to treat schizophrenia, the manic phase of bipolar disorder, and agitated behavior. They are also used as preanesthetics and to treat drug-associated delirium and hallucinations, nausea, vomiting, headaches, hiccups, pruritus, Tourette's syndrome, and a variety of extrapyramidal movement disorders (e.g., chorea, dystonias, hemiballismus, spasms, tics, torticollis). Antipsychotics are a structurally diverse group of heterocyclic compounds; more than 50 different drugs are available for clinical use worldwide with numerous others in various stages of development. Classes include benzamide, benzepine, butyrophenone (phenylbutylpiperidine), dibenzo-oxepino pyrrole, diphenylbutylpiperidine, indole, phenothiazine, quinolinone, rauwolfia alkaloid, and thioxanthene derivatives (Table 124.1). The phenothiazine and thioxanthene classes are further subdivided into three groups (aliphatic, piperazine, and piperidine) based on central ring side-chain substitution.

Although traditionally classified by structure, antipsychotics are more ideally classified by pharmacologic profile. Each agent has a unique receptor-binding profile (Table 124.2), and this profile can be used to predict adverse effects in both therapeutic and overdose situations [1–3]. Clinical toxicity is the result of exaggerated pharmacologic activity. Antipsychotics are also classified as *typical* or *atypical* (Tables 124.1 and 124.2). Traditional or conventional antipsychotics, which readily produce extrapyramidal signs and symptoms (EPS) at antipsychotic doses, are considered typical. Newer agents that have minimal extrapyramidal side effects at clinically effective antipsychotic doses are effective for treating the negative symptoms (e.g., alogia, avolition, social withdrawal, flattened affect) of schizophrenia and have a low propensity to cause tardive dyskinesia with long-term treatment are considered atypical [1–4]. The characterization of antipsychotics as typical or atypical is ultimately determined by receptor binding. One or more of several different receptor-binding characteristics are associated with drug atypia, and each agent is atypical for different reasons [4,5]. Understanding how specific receptor-binding characteristics produce clinical effects has facilitated the development of antipsychotics that separate antipsychotic activity from other activity, thus minimizing adverse effects and maximizing patient compliance.

Antipsychotic toxicity may occur as an idiosyncratic reaction during therapeutic use or following accidental or intentional overdose. Central nervous system (CNS) and cardiovascular disturbances are the most common dose-related toxic manifestations, but other effects include the anticholinergic syndrome (see Chapter 121) and various extrapyramidal syndromes. Therapeutic use has been associated with agranulocytosis, aplastic anemia, diabetes mellitus, hepatotoxicity, hypertriglyceridemia, fatal myocardial infarction, myocarditis, neuroleptic malignant syndrome (see Chapter 66), pancreatitis, seizures, sleep apnea, sudden infant death syndrome, sudden adult death, venous thromboembolism, and vasculitis [21–29]. Most deaths are the consequence of suicidal overdose by psychotic or depressed adults and frequently involve mixed ingestions or ingestion of the agents chlorpromazine, loxapine, mesoridazine, quetiapine, or thioridazine [30,31]. Because of a large toxic to therapeutic ratio for most antipsychotics, fatalities rarely occur. In 2007, there were 46,239 antipsychotic exposures reported to United States poison centers, of which 41,607 (90%) were due to atypical agents and 4,632 (10%) were due to phenothiazines [32]. Major toxicity and death occurred in 1.1% and 0.02% of atypical agent exposures, and in 0.8% and 0.04% of phenothiazine exposures. From this data, death occurred in less than four patients for every 1,000 antipsychotic agent toxic exposures. Quetiapine was most commonly associated with fatality in both mixed and single substance ingestions but this may reflect usage pattern and not individual agent toxicity [32]. From another study, the most toxic antipsychotics result in death from poisoning for every 100 patient-years of use [30]. Dose-related effects are most pronounced in nonhabituated patients at the extremes of age.

Recent data has demonstrated that users of antipsychotic drugs have higher rates of sudden cardiac than do nonusers and former users of antipsychotic drugs [6]. The increased risk of sudden cardiac death is similar in magnitude for both typical and atypical agents, with adjusted incidence-rate ratios of 1.99 and 2.26, respectively, when compared with nonusers. For both classes of drugs, the risk of sudden cardiac death increases significantly with an increasing dose. Users of clozapine and thioridazine had the greatest increased of sudden cardiac death, with an adjusted incidence rate that was more than three times that for nonusers.

PHARMACOLOGY

Antipsychotics bind to and antagonize presynaptic (autoreceptors) and postsynaptic type 2 dopamine (D_2) receptors in the CNS and peripheral nervous system [7]. Initially, dopamine neurons increase the synthesis and release of dopamine in response to autoreceptor antagonism. With repeated dosing, however, depolarization inactivation of the neuron occurs, and decreased synthesis and release of dopamine occur despite ongoing postsynaptic receptor blockade [7,8].

All antipsychotics produce their therapeutic antipsychotic effect from mesolimbic D_2-receptor antagonism. D_2-receptor affinity (potency) in this region strongly correlates with the daily therapeutic dose (see Table 124.1) [1,4,9]. Simultaneous antagonism of other D_2 receptors produces additional clinical effects, the majority of which are undesirable. Mesocortical receptor blockade appears to create cognitive impairment and further worsens the negative symptoms of schizophrenia [10]. Excessive D_2-receptor blockade in mesocortical and mesolimbic areas, as occurs after neuroleptic overdose, may partly mediate CNS depression from these agents. Antagonism of nigrostriatal D_2-receptors produces EPS (e.g., acute dystonia, akathisia, parkinsonism). D_2-receptor potency in nigrostriatal relative to mesolimbic areas correlates with the likelihood of developing EPS [1,2,4,11,12]. Typical antipsychotics antagonize basal ganglia D_2 receptors in the same dose range necessary for limbic D_2-receptor blockade, thus creating high EPS liability [11,12]. The high-potency or typical agents (i.e., fluphenazine,

TABLE 124.1

CLASSIFICATION AND DOSING OF NEUROLEPTIC AGENTS

Structural class	Generic name (trade name)	Affinity of neuroleptic agent for dopamine (D_2) receptor (potency)[a]	Daily dose range (mg)
Typical agents			
Butyrophenone (phenyl-butylpiperidine)	Droperidol (Inapsine)	3+	1.25–30
	Haloperidol (Haldol)	2+	1–30
	Other: benperidol, bromperidol, melperone, pipamperone, trifluperidol[c]		
Diphenylbutylpiperidine	Pimozide (Orap)	2+	1–20
	Other: fluspirilene, penfluridol[c]		
Indole	Molindone (Moban)	1+	15–225
	Other: oxypertine[c]		
Phenothiazine			
Aliphatic	Chlorpromazine (Thorazine)	2+	25–2,000
	Promazine (Sparine)[b]	—	50–1,000
	Promethazine (Phenergan)	2+	25–150
	Triflupromazine (Vesprin)	—	5–90
Piperazine	Acetophenazine (Tindal)	—	40–400
	Fluphenazine (Prolixin)	3+	0.5–30
	Perphenazine (Trilafon)	3+	4–64
	Prochlorperazine (Compazine)	2+	10–150
	Trifluoperazine (Stelazine)	3+	2–40
	Thiethylperazine (Torecan)	—	10–30
Piperidine	Mesoridazine (Serentil)	2+	30–400
	Thioridazine (Mellaril, Millazine)	2+	20–800
	Other: diethazine, ethopropazine, levomepromazine, perazine, pipotiazine thiopropazate, thioproperazine, pericyazine[c]		
Thioxanthene	Chlorprothixene (Taractan)	2+	30–600
	Clopenthixol[c]	—	—
	Flupenthixol[c]	3+	4
	Thiothixene (Navane)	3+	6–60
	Zuclopenthixol (Cisordinol, Clopixol)[c]	3+	10–50
Atypical agents			
Benzamides	Amisulpride[c]	2+	100–1,200
	Raclopride[c]	3+	5–8
	Remoxipride[c]	1+	150–600
	Sulpiride[c]	2+	100–1,600
	Sultopride[c]	2+	100–1,200
	Trimethobenzamide (Tigan)[b]	—	100–600
	Other: epidepride, eticlopride levosulpiride, nemonapride, tiapride[c]		
Benzepine			
Dibenzodiazepine	Clozapine (Clozaril, Leponex)	1+	150–900
Dibenzo-oxazepine	Loxapine (Loxitane)	1+	20–250
Thienobenzodiazepine	Olanzapine (Zyprexa)	2+	5–20
Dibenzothiazepine	Quetiapine (Seroquel)	1+	300–600
Dibenzothiazepine	Zotepine[c]	2+	100–300
	Other: butaclamol, fluperlapine, clothiapine, metiapine, savoxepine[c]		
Indole			
Benzisoxazole	Risperidone (Risperdal)	3+	2–16
	Paliperidone (Invega)	3+	3–12
Imidazolidinone	Sertindole (Serlect)[c]	3+	12–24
Benzisothiazole	Ziprasidone (Zeldox)	3+	40–160
	Other: iloperidone[c]		
Pyrrole	Asenapine (Saphris)	3+	10–20
Quinolinone	Aripiprazole (Abilify, Abitat)	3+	10–30
	Bifeprunox[c]		

[a] A higher numerical value indicates greater binding affinity (greater antagonism) at D_2 receptor. Binding affinity (potency) at D_2 receptor correlates with daily dose range.
[b] Antiemetic only.
[c] Not available for clinical use in the United States.
0, minimal to none; 1+, low; 2+, moderate; 3+, high to very high.

TABLE 124.2

RELATIVE NEURORECEPTOR AFFINITIES FOR NEUROLEPTICS[a]

Neuroleptic agent	Receptor					
	H_1 Histaminergic	α_1-Adrenergic	α_2-Adrenergic	M_1 muscarinic	5-HT_{2A} serotonergic	EPS risk[b]
Typical agents						
Chlorpromazine	2+	3+	0	1+	3+	1+
Fluphenazine	0	0	0	0	0	3+
Haloperidol	0	1+	0	0	1+	3+
Loxapine	3+	3+	0	2+	3+	1+
Mesoridazine	3+	3+	–	1+	–	1+
Molindone	0	0	1+	0	0	3+
Perphenazine	1+	1+	0	0	–	3+
Pimozide	0	1+	–	0	1+	3+
Prochlorperazine	1+	1+	0	0	0	3+
Thioridazine	2+	3+	0	3+	2+	1+
Thiothixene	0	0	0	0	0	3+
Trifluoperazine	0	1+	0	0	1+	3+
Atypical agents						
(Ami)sulpiride	0	0	0	0	0	1+
Asenapine	3+	2+	2+	0	3+	1+
Aripiprazole	2+	2+	0	0	3+	0
Clozapine	3+	3+	3+	3+	3+	0
Olanzapine	2+	2+	0	3+	3+	0
Paliperidone	1+	2+	1+	0	3+	1+[c]
Quetiapine	3+	3+	0	3+	1+	0
Remoxipride	0	0	0	0	0	1+
Risperidone	1+	2+	1+	0	3+	1+[c]
Sertindole	0	1+	0	0	3+	0
Ziprasidone	0	3+	0	0	3+	1+
Zotepine	2+	0	2+	0	3+	1+

[a]Relative neuroreceptor affinity [neuroreceptor affinity at receptor X/dopamine (D_2)-receptor affinity] indicates relative receptor antagonism at therapeutic (D_2-blocking) antipsychotic doses.
[b]A higher M_1 and 5-HT_2 relative neuroreceptor affinity confers a lower EPS risk.
[c]Dose-dependent incidence of extra EPS.
Adapted from references [1–20].
0, minimal to none; 1+, low; 2+, moderate; 3+, high; 4+, very high; EPS, extrapyramidal side effects.

haloperidol, perphenazine, thiothixene, and trifluoperazine) are most commonly associated with EPS [1]. Atypical agents have low D_2-receptor potency and occupancy (i.e., clozapine, olanzapine, quetiapine) at therapeutic doses, are partial D_2-receptor agonists (e.g., aripiprazole), or are more site selective (i.e., sulpiride, raclopride) and preferentially antagonize limbic D_2 receptors [2–4,8,13]. Thus, they are less likely to cause EPS or worsen negative symptoms of schizophrenia at therapeutic doses.

D_2-receptor blockade in the anterior hypothalamus (preoptic area) may alter core temperature set point and block thermosensitive neuronal inputs and thermoregulatory responses [7]. Hypothermia or hyperthermia may result. D_2-receptor blockade in the pituitary (tuberoinfundibular pathway) results in sustained elevated prolactin secretion, which may cause galactorrhea, gynecomastia, menstrual changes, and sexual dysfunction (impotence in men) [1,11]. The antiemetic activity of antipsychotics results from similar inhibition of dopaminergic receptors in the chemoreceptor trigger zone (area postrema) of the medulla oblongata [7]. Antagonism of dopamine receptors present on peripheral sympathetic nerve terminals and vascular smooth muscle cells may produce autonomic dysfunction (i.e., tachycardia, hypertension, diaphoresis, pallor) [7,33–35]. Simultaneous blockade of D_2 receptors in the hypothalamus, striatum, mesocortical and mesolimbic areas, peripheral sympathetic nerve terminals, and vasculature mediate the neuroleptic malignant syndrome in susceptible individuals (see Chapter 66).

In addition to D_2 receptors, antipsychotics are competitive antagonists at a wide range of neuroreceptors; varied binding affinities exist at α-adrenergic ($\alpha_{1,2}$), dopaminergic (D_{1-5}), histaminergic (H_{1-3}), muscarinic (M_{1-5}), and serotonergic (5-HT_{1-7}) receptors (see Table 124.2) [1,4,12]. The neuroreceptor-binding profile for each agent predicts clinical effects. The ratio of other neuroreceptor-binding affinities to D_2-receptor–binding affinity (relative binding affinity) predicts the likelihood of producing those receptor-mediated effects at clinically effective antipsychotic (D_2-blocking) doses and in overdose [1,12]. A ratio similar to or greater than 1 makes other receptor-mediated effects likely. High relative α_1-adrenergic antagonism (i.e., aliphatic and piperidine phenothiazines, asenapine, clozapine, olanzapine, risperidone, ziprasidone) correlates with the incidence and severity of orthostatic hypotension, reflex tachycardia, nasal congestion, and miosis [11]. Significant relative α_2-adrenergic blockade, as occurs with asenapine, clozapine, paliperidone, and risperidone, may result in sympathomimetic effects (e.g., tachycardia). High relative H_1-receptor blockade (e.g., aliphatic and piperidine phenothiazines, asenapine, clozapine, olanzapine, quetiapine) produces sedation, appetite stimulation, and hypotension [1,11]. Relative potency at M_1 receptors correlates directly with anticholinergic effects (i.e., tachycardia, hypertension, mydriasis, blurred vision, ileus, urinary retention, dry skin and mucous membranes, cutaneous flushing, sedation, memory dysfunction, hallucinations, agitation, delirium, and hyperthermia) and inversely with the incidence of extrapyramidal

reactions [1]. Olanzapine, clozapine, and aliphatic and piperidine phenothiazines are associated with clinically significant anticholinergic effects. The ability of clozapine to produce sialorrhea is likely mediated by its partial agonism at M_1 and M_4 receptors [1]. High relative antagonism at 5-HT_{1A} and 5-HT_{2A} receptors appears to predict a low EPS risk [1,7,36,37]. The clinical effects that occur with other neuroreceptor subtype binding are not well understood.

The advent of atypical agents, which provide an improved motor side effect profile, marks significant progress in neuroleptic development. Atypical agents may be subdivided into four functional groups: (a) the D_2-, D_3-receptor antagonists (i.e., amisulpride, raclopride, remoxipride, and sulpiride); (b) the D_2-, $5HT_{2A}$-, and α_1-receptor antagonists (i.e., paliperidone, risperidone and ziprasidone); (c) the broad-spectrum, multireceptor antagonists (i.e., asenapine, clozapine, olanzapine, quetiapine); and (d) the D_2-, 5-HT_{1A}-receptor partial agonists (i.e., aripiprazole, bifeprunox), also known as dopamine and serotonin system stabilizers [3] (see Table 124.2). One or more of several different pharmacologic mechanisms define drug atypia. Low D_2-receptor potency (high-milligram dosing), low (less than 70%) D_2-receptor occupancy in mesolimbic and nigrostriatal areas at therapeutic drug doses, partial agonist activity at D_2 receptors, selective mesolimbic D_2-receptor antagonism, and high D_1-, D_4-, M_1-, $5HT_{1A}$-, $5HT_{2A}$-receptor potencies relative to D_2-receptor–binding are pharmacologic characteristics that alone or in combination may be responsible for the atypical nature of these agents [1–3,7,13,36,37]. Conversely, typical antipsychotics are characterized by high D_2-receptor potency (low-milligram dosing) and a narrow receptor profile in the brain [1]. Unlike typical agents, atypical agents also appear to have a minimal propensity to elevate serum prolactin concentrations.

Serotonin antagonism enhances antipsychotic efficacy and reduces the incidence of EPS [36,37]. $5HT_{2A}$-receptor antagonism in the striatum and prefrontal cortex offsets neuroleptic-induced D_2-receptor blockade and reduces EPS and negative symptoms of schizophrenia, respectively [7,10,36–38]. $5HT_{2A}$-receptor antagonism also increases serotonin levels in the limbic system, which may have a direct antipsychotic effect [7,10]. Drugs with high relative $5HT_{2A}$-receptor antagonism as compared to D_2-receptor antagonism (i.e., amperozide, asenapine, clozapine, olanzapine, paliperidone, risperidone, ziprasidone) can be given in smaller clinically effective antipsychotic doses and thus have a smaller risk of inducing EPS [1,11,38,39]. In addition, antipsychotics that stimulate $5HT_{1A}$ autoreceptors in the striatum (i.e., aripiprazole, clozapine, ziprasidone) reduce striatal D_2-receptor blockade, thereby decreasing the likelihood of EPS [8,36,37].

Aliphatic and piperidine phenothiazines (e.g., chlorpromazine, thioridazine, mesoridazine) have local anesthetic, quinidine-like (type Ia) antiarrhythmic, and myocardial depressant effects [7]. These agents block both fast-sodium channels responsible for myocardial membrane depolarization [40]. Sodium channel blockade is voltage and frequency dependent; blockade is augmented at less negative membrane potentials and faster heart rates [40]. Thus, the anticholinergic properties (e.g., tachycardia) and tissue acidemia-producing effects (e.g., seizures, hypotension) of these drugs potentiate their sodium channel blocking effects. Although specifically demonstrated for sertindole and thioridazine only, all neuroleptics appear to variably antagonize delayed-rectifier, voltage-gated, potassium channels responsible for myocardial membrane repolarization; antagonism occurs specifically at the potassium channel encoded by the human ether-a-go-go (*hERG*) gene [41,42]. Potassium-channel blockade is concentration-, voltage-, and reverse-frequency dependent; blockade is increased at higher tissue concentrations, less negative membrane potentials, and slower heart rates [41,42]. Potassium channel blockade may result in early after depolarizations and subsequent torsade de pointes (TdP)–type ventricular tachycardia. Haloperidol, mesoridazine, thioridazine, and pimozide share an added property of calcium channel blockade [43,44].

Electrophysiologic effects variably include a depressed rate of phase 0 depolarization, depressed amplitude and duration of phase 2, and prolongation of phase 3 repolarization. Ventricular repolarization abnormalities, such as T-wave changes (blunting, notching, inversion), increased U-wave amplitude, and prolongation of the QT interval, are the earliest and most consistent electrocardiographic changes produced by neuroleptics [45–48]. Dose-related prolongation of the QT interval has been described with droperidol, haloperidol, loxapine, phenothiazines, pimozide, quetiapine, risperidone, sertindole, and ziprasidone [31,41,42,45–57]. Conduction disturbances (i.e., bundle-branch, fascicular, intraventricular, and atrioventricular [AV] blocks) and supraventricular and ventricular tachyarrhythmias (i.e., monomorphic and polymorphic TdP ventricular tachycardia, ventricular fibrillation) have been reported [31,49,57–61]. Cardiac effects are dose and concentration dependent but can occur with therapeutic as well as toxic doses. Ventricular tachyarrhythmias and asphyxia (due to seizures, aspiration, or respiratory depression) have been postulated as etiologies of sudden death for patients taking therapeutic doses of antipsychotics, particularly phenothiazines [29,62].

Antipsychotics produce dose-related electroencephalographic changes, and some agents have been shown to lower the seizure threshold [26,27,63–66]. The risk of seizures is dose related, and thus, greatest after overdose [27,65,66]. Chlorpromazine, clozapine, and loxapine are the most likely agents to produce seizures [26,27,54,63–66]. Most other agents, however, are uncommonly associated with seizures, even after overdose. The mechanism by which antipsychotics produce seizures is not well understood but likely involves dose-related blockade of norepinephrine reuptake, antagonism of gamma-aminobutyric acid type A receptors, and altered neuronal transmembrane ionic currents.

Antipsychotics have a relatively flat dose-response curve. Effective therapeutic doses vary over a wide range (see Table 124.1). The optimal dose is determined by the clinical response, not by serum drug levels. Pharmacologic effects generally last 24 hours or more, allowing for once-daily dosing. Tablet, capsule, and liquid oral preparations, suppository, and injectable immediate-release and sustained-release (depot) solutions are available [7]. Oral preparations include both rapidly disintegrating (sublingual absorption) and sustained-release formulations. Paliperidone, the active metabolite of risperidone, is commercially available in an extended-release oral preparation (Invega®). Following a single dose, plasma concentrations gradually rise and do not peak until approximately 24 hours after dosing [67]. Slow-release, highly lipophilic depot formulations (i.e., fluphenazine enanthate and decanoate, haloperidol decanoate, paliperidone palmitate) for intramuscular injection are created by esterifying the hydroxyl group of an antipsychotic with a long-chain fatty acid and dissolving it in a sesame oil vehicle. A long-acting formulation of risperidone (Risperdal Consta®) is available that contains an aqueous suspension of risperidone mixed with a biodegradable carbohydrate copolymer.

Antipsychotic pharmacokinetics are complex and incompletely understood [7]. When administered orally, they are well absorbed, but bioavailability is unpredictable (range: 10% to 70%) due to large interindividual variability and presystemic (hepatic and intestinal) metabolism [7,68,69]. After parenteral administration, drug bioavailability is 4 to 10 times greater than with oral dosing because of the absence of first-pass metabolism [7,68,69]. Hence, therapeutic intravenous (IV) or intramuscular (IM) doses are substantially less than oral ones. Plasma concentrations peak 1 to 6 hours after therapeutic oral and sublingual dosing, 30 minutes to 1 hour after immediate-release IM injection, and within 24 hours after oral

dosing of extended-release preparations. After a single intramuscular dose of a depot preparation, plasma concentrations peak variably from a few days to over 2 weeks after initial injection. [67–69]. After oral overdose, absorption should occur more rapidly (first-order kinetics), but peak plasma concentrations are delayed, as more time is required for complete absorption. As a result, clinical effects are expected to occur sooner and last longer. Erratic absorption may occur after ingestion of agents with significant anticholinergic effects.

After absorption, antipsychotics are highly bound to plasma proteins (75% to 99%) [7,68,69]. However, because they are also highly lipophilic, volumes of distribution are large (10 to 40 L per kg) and serum drug levels after therapeutic doses are quite low (one to several hundred ng per mL). These pharmacokinetic characteristics make extracorporeal removal by hemodialysis or hemoperfusion impractical. Antipsychotics tend to accumulate in the brain, easily cross the placenta, and are found in breast milk [7]. Elimination occurs slowly and extensively by hepatic metabolism, with serum concentration half-lives averaging 20 to 40 hours. Depot antipsychotics have an apparent elimination half-life of 1 to 3 weeks due to slow tissue absorption [68]. Small amounts (1% to 3%) are excreted unchanged by the kidney. As a rule, hepatic metabolism yields multiple metabolites, some of which are pharmacologically active and likely to extend parent drug effects after therapeutic or toxic dosing [70,71]. Metabolites are eliminated by urinary and biliary excretion and can be detected in the urine for several days after a single ingestion and for a month or more after cessation of long-term therapy [7,69]. Large interindividual variations in the metabolism of neuroleptics result in significant differences in steady-state plasma concentrations with fixed, therapeutic dosing [7,68,69,72]. There is often little correlation between neuroleptic dose, serum concentrations, and clinical effects.

Renal insufficiency may rarely result in drug accumulation and toxicity [73]. Renal excretion accounts for a significant proportion of total drug elimination for the benzamide (e.g., remoxipride, sulpiride) and benzisoxazole derivatives (e.g., paliperidone, risperidone) [67–69]. Thus, dose alteration is recommended for patients with renal insufficiency who regularly take these agents. Other neuroleptics, however, do not routinely require dose alteration for patients with renal impairment. Dose adjustment is also recommended for those patients who have a diminished ability to clear neuroleptics, such as the elderly and those with significant hepatic disease or specific cytochrome P450 enzyme deficiencies (i.e., CYP2D6, CYP1A2) [7,69]. Most antipsychotics are pregnancy category C and should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Breast feeding is not recommended for women taking neuroleptics because most neuroleptics are secreted into breast milk, and their safety in infants is not established.

The majority of patients who take an accidental or intentional overdose of an antipsychotic agent remain asymptomatic or develop only mild toxicity [5,32]. Toxic effects result from exaggerated pharmacologic activity and include CNS and consequent respiratory depression, miosis or mydriasis, cardiovascular abnormalities, agitation, confusion, delirium, anticholinergic stigmata, seizures, EPS, and myoclonic jerking. Hypothermia and, less commonly, hyperthermia have occurred. Hypothermia may result from α_1-adrenergic–mediated peripheral vasodilation at low ambient temperature, hypotension, coma, loss of shivering capabilities, and disrupted hypothalamic thermoregulation. Peripheral vasodilation at high ambient temperature, seizures, neuromuscular agitation, loss of sweating capabilities, and hypothalamic dysfunction may contribute to hyperthermia. Seizures are uncommon and occur mainly in patients with underlying epilepsy and those with clozapine and loxapine overdoses. In one study of 299 patients with neuroleptic overdose, the incidence of seizure was only 1% [31]. Rhabdomyolysis, myoglobinuria, and acute renal failure may occur after prolonged convulsions [65,74]. CNS depression is the most frequent clinical finding after neuroleptic overdose [31,75–79]. Sinus tachycardia and orthostatic hypotension are the most frequent cardiovascular findings [31,75–79]. Other cardiovascular effects include hypertension, cardiac conduction disturbances, tachyarrhythmias, bradyarrhythmias, and, rarely, pulmonary edema [80,81]. Anticholinergic stigmata (see Chapter 121) may occur after overdose with aliphatic and piperidine phenothiazines, clozapine, and olanzapine [5,76,79,82–86].

Of the thousands of antipsychotic overdoses reported each year, less than 1% result in fatal toxicity [30,32]. Fatality is most often due to respiratory arrest before medical intervention, arrhythmias, or aspiration-induced respiratory failure [5,7,29,32]. Toxic and lethal doses are highly variable and are influenced by the agent ingested, the presence of coingestants and comorbid illness, the age and habituation of the patient, and the time to treatment. Nonhabituated patients at the extremes of age are more sensitive to the toxic effects of these drugs than those who have taken this drug chronically before an acute overdose. The ingestion of a single tablet of chlorpromazine, clozapine, loxapine, mesoridazine, olanzapine, quetiapine, or thioridazine may cause CNS and respiratory depression in young children [5,73,74,84]. Death of an infant was reported after the ingestion of only 350 mg of chlorpromazine. Adult fatalities have been reported after ingestions of 2.0 g of clozapine and chlorpromazine, 2.5 g of loxapine and mesoridazine, 1.5 g of thioridazine, and 600 mg of olanzapine [87,88]. Many patients, however, have survived much higher ingestions. In general, acute ingestion of greater than twice a maximal therapeutic dose is potentially serious.

Unintended adverse effects that occur during therapeutic use may be idiosyncratic or dose related, occur early or late during the course of therapy, or result from interactions with other drugs, and are often due to receptor antagonism. The major adverse side effect, both in terms of prevalence and in terms of the distress that it causes, is the tendency to induce extrapyramidal dysfunction.

Extrapyramidal syndromes are a group of movement disorders that result from the interference with neurotransmitter (primarily D_2-receptor blockade) function in the basal ganglia. EPS occur in up to 75% of patients treated with low-milligram, high-potency traditional agents (e.g., fluphenazine, haloperidol, thiothixene), but an incidence not significantly different from placebo (< 5%) has been described with newer atypical agents (e.g., aripiprazole, clozapine, olanzapine, quetiapine) [89–91]. EPS may occur early (i.e., within a few hours to days), at an intermediate stage (i.e., a few days to months) or late (i.e., after > 3 months) in the course of therapy. Early EPS include acute dyskinesia (acute dystonic reactions), intermediate syndromes include akathisia and parkinsonism, and late disorders include tardive dyskinesia, tardive dystonia, and focal perioral tremor (rabbit syndrome). EPS are more commonly associated with therapeutic doses of neuroleptics but may follow acute overdose (e.g., acute dystonic reactions [ADRs]), particularly in children [5,75,92]. Only ADRs, the acute syndrome most likely to develop in the intensive care unit, are discussed.

ADRs are reversible motor disturbances consisting of sustained, uncoordinated, and involuntary spasmodic movements of various muscle groups. Although ADRs most often occur after administration of therapeutic doses of antipsychotics [93], they have also been described after administration of antihistamines (both H_1- and H_2-blockers), anticholinergics (e.g., benztropine, diphenhydramine), anticonvulsants (e.g., carbamazepine, phenytoin), calcium channel blockers (e.g., nifedipine, verapamil), metoclopramide, cyclic antidepressants (e.g., amitriptyline, amoxapine, doxepin, imipramine),

selective serotonin reuptake inhibitors (e.g., fluoxetine, sertraline), monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine), anesthetic induction agents (e.g., ketamine, etomidate, thiopental), cholinergics (e.g., bethanechol, insecticides), and cocaine. ADRs can also occur as a primary (non–drug-related) disorder [94].

The pathophysiology of ADRs is not fully elucidated but involves a disruption of cholinergic (interstriatal) and dopaminergic (nigrostriatal) pathways in the basal ganglia. Normally, dopamine is an excitatory neurotransmitter and acetylcholine is an inhibitory neurotransmitter [95]. Normal balance between these closely linked pathways is necessary for coordinated muscular activity. Dopaminergic D_1-, gamma-aminobutyric acid- (striatonigral), glutaminergic- (corticostriatal), noradrenergic-, $5HT_{1A}$- and $5HT_{2A}$- (raphe-striatal and raphe-nigral), and sigma (σ)- (red nucleus, substantia nigra, and cranial nerve motor nuclei) receptor inputs modulate this balance [7,8,36,37,96,97]. Blockade of striatal D_2 receptors by high-potency neuroleptics disrupts the dopaminergic–cholinergic balance in favor of cholinergic excess, and dystonia results [98,99]. Agents that balance D_2-receptor antagonism with D_1-, M_1-, or $5HT_{2A}$-receptor antagonism or $5HT_{1A}$-receptor agonism prevent striatal cholinergic excess and are less likely to precipitate acute dystonia [1,14,36,37,100]. Gamma-aminobutyric acid–receptor affinity correlates inversely, whereas σ- and *N*-methyl-d-aspartate-glutamate receptor–binding affinities correlate directly with the clinical incidence of acute dystonia [8,96,97].

Paradoxically, ADRs may also result from hyperdopaminergic function induced by D_2-receptor blockade in the basal ganglia [101,102]. Acute D_2-receptor blockade may stimulate increased dopamine synthesis and release from nigrostriatal neurons and postsynaptic receptor upregulation (supersensitivity). As brain concentration of drug declines hours to days after a dose, a state of dopamine excess develops, and dystonia results [101,102].

ADRs usually occur soon after initiation of therapy or after an increase in dose. Fifty percent of ADRs occur within 48 hours of initiating therapy, and 90% within 5 days [103–105]. Peak incidence occurs when drug levels are declining in the serum. Although the absolute incidence of ADRs is unknown, they are estimated to occur in 25% of patients treated with IM depot preparations, 16% of patients who have been given haloperidol, 8% of patients treated with thiothixene, 2% to 12% of all patients who take phenothiazines, 3.5% of patients treated with chlorpromazine, and 1% or less in patients taking atypical agents [11,88,98,103,104]. Phenothiazines that contain a piperazine side chain (i.e., prochlorperazine, trifluoperazine, perphenazine, fluphenazine, and acetophenazine) are associated with a higher incidence of dystonic reactions than are other phenothiazines [103]. Atypical agents (particularly clozapine) are unequivocally associated with a reduced incidence of ADRs [11]. The likelihood of an ADR is more dependent on individual susceptibility than on neuroleptic structure, potency, dose, and duration of therapy [106]. ADRs most commonly occur in men, patients 5 to 45 years of age (particularly those younger than 15 years old), and those with a personal or family history of dystonia or a recent history of drug (i.e., cocaine) or alcohol abuse [103–105,107].

Seizures are an uncommon side effect of certain antipsychotics (e.g., clozapine, chlorpromazine, loxapine). They typically occur at higher therapeutic doses and after overdose in susceptible patients. Seizures are usually generalized and of the major motor type. Clozapine, the most epileptogenic agent at therapeutic dosing, is associated with a seizure rate of approximately 1% at doses lower than 300 mg per day, a rate of 2.7% at doses between 300 and 600 mg per day, and a rate of 4.4% with doses larger than 600 mg per day [64,65]. A cumulative seizure risk of 10% after 3.8 years of treatment has been demonstrated with clozapine [79,80]. Newer, atypical agents show no increase in seizure risk when compared with haloperidol or placebo [26]. Other risk factors for seizures include a history of organic brain disease, epilepsy, electroconvulsive therapy, abnormal baseline electroencephalogram, polypharmacy, and initiation and rapid dose titration of neuroleptics [26,66]. After overdose, the incidence of seizures is as high as 60% and 10% for loxapine and clozapine, respectively, whereas the incidence for most other neuroleptics is approximately 1% [5,31,54,76].

Agranulocytosis (absolute neutrophil count < 500 cells per mm^3) is a serious idiosyncratic side effect of clozapine and phenothiazine therapy. It is rare (0.1 to 1.0 per 1,000 persons) with phenothiazines and usually occurs in the first 12 weeks of therapy [108,109]. A cumulative risk of 0.91% (9 per 1,000 persons) at 18 months is reported with clozapine; more than 80% of cases occur in the first 3 months [21,110]. Initial mortality rates associated with agranulocytosis ranged from 30% to 85%, but with regular white blood cell count monitoring and treatment with granulocyte colony stimulating factor (G-CSF), mortality rates have dropped to 3% to 4% [21,110,111]. The mechanism underlying clozapine-induced agranulocytosis may be both immune-mediated and the result of direct myelotoxicity from the drug [112]. Granulocyte colony-stimulating factor has been useful in treatment, halving recovery time from 16 to 8 days [113,114]. Agranulocytosis has not been reported after acute overdose. Neutropenia has also been associated with the therapeutic use of olanzapine, quetiapine, and risperidone [115–117].

Hepatic transaminitis is an adverse side effect of most antipsychotics [11,23]. Hepatotoxicity is idiosyncratic, often occurs within the first 3 months of treatment, and is usually mild and self-limiting (most patients remain asymptomatic). The patterns of hepatoxicity are both hepatitic (including nonalcoholic steatohepatitis) and cholestatic [118,119].

Most atypical neuroleptics result in an increased appetite and weight gain. More importantly, and perhaps causally related, the therapeutic use of atypical agents has been associated with an increased risk of developing type II diabetes mellitus [107–124]. Several cases of fatal diabetic ketoacidosis and hyperglycemia hyperosmolar nonketotic coma have been reported in patients taking clozapine and olanzapine [124–126]. Pancreatitis has been associated with the use of clozapine, and hypertriglyceridemia has been reported in patients treated with clozapine, olanzapine, and quetiapine [106,127–130].

Allergic dermatitis, cholestatic jaundice, irreversible pigmentary retinopathy, photosensitivity reactions, and priapism are uncommon idiosyncratic reactions associated with phenothiazine therapy [11,23,131–134]. Myocarditis and cardiomyopathy have been rarely associated with the use of clozapine; these conditions are idiosyncratic, frequently fatal, often occur within the first 2 weeks of treatment, and are likely the result of acute hypersensitivity [25,135,136].

Drug interactions and adverse effects may be pharmacodynamic (i.e., receptor or channel mediated) or pharmacokinetic (i.e., altered absorption, metabolism, or protein binding) [137,138]. Combining antipsychotics with other CNS depressants (i.e., antihistamines, cyclic antidepressants, ethanol, opiates, sedative–hypnotics) may produce enhanced CNS and respiratory depression. Respiratory depression and arrest has been reported with the coadministration of clozapine and lorazepam or diazepam [139–142]. Exaggerated anticholinergic effects may occur with concurrent use of tricyclic antidepressants, certain skeletal muscle relaxants, antihistamines, and antiparkinson agents. The combination of antipsychotics with significant α_1-adrenergic blockade and certain antihypertensive agents (e.g., hydralazine, prazosin) may precipitate hypotension. Enhanced cardiotoxicity may occur when mesoridazine or thioridazine is combined with type IA

antiarrhythmic agents or tricyclic antidepressants. High-dose droperidol, haloperidol, sertindole, thioridazine, and ziprasidone may potentiate QT prolongation produced by other cardioactive agents.

Most antipsychotic agents are extensively metabolized by the hepatic cytochrome P450 (CYP) enzyme system, particularly the CYP2D6 and CYP1A2 isoenzymes. Other drugs that are substrates (i.e., cyclic antidepressants), inhibitors (i.e., cimetidine, erythromycin, selective serotonin reuptake inhibitors), or inducers (i.e., anticonvulsants) of similar CYP isoenzymes may alter antipsychotic metabolism and precipitate adverse effects. These interactions often go unnoticed, but they may be clinically significant. Cimetidine, erythromycin, and fluvoxamine have precipitated clinical clozapine toxicity from hepatic CYP1A2 isoenzyme inhibition [143–146]. Paroxetine may precipitate risperidone toxicity from CYP2D6 isoenzyme inhibition. Knowledge of antipsychotic-associated drug interactions facilitates recognition and treatment of these increasingly common iatrogenic events.

CLINICAL TOXICITY

Acute overdose may result in nausea and vomiting soon after ingestion. CNS and cardiovascular effects, however, usually dominate the clinical picture [5,31,55–58,61,75–79]. In mild intoxication, findings include ataxia, confusion, lethargy, slurred speech, tachycardia, and hypertension or orthostatic hypotension. Anticholinergic signs (e.g., dry skin and mucosa, decreased bowel sounds, urinary retention) and hyperreflexia may also be present. Although usually considered an idiosyncratic reaction, EPS (e.g., ADRs) have been described after acute neuroleptic overdose, particularly in children [5,75,92]. Electrocardiographic changes such as prolonged PR and QT intervals, ST-segment depression, T-wave abnormalities (biphasic, blunting, inversion, notching, widening), and increased U waves may be seen [31,45–48]. Other than sinus tachycardia, repolarization abnormalities are the earliest and most common electrocardiographic findings associated with neuroleptic poisoning [31,45–48,52,147].

Signs and symptoms of moderate poisoning include low-grade coma (see Chapter 117), respiratory depression, and hypotension. Miosis or mydriasis may occur. Miosis is more likely to occur following overdose of both atypical and typical agents; it has been described in 75% of adults and 72% of children after phenothiazine overdose [5,77,79,84,148]. Internuclear ophthalmoplegia has been reported [149]. Paradoxical agitation, delirium, hallucinations, psychosis, myoclonic jerking, and tachypnea may occur [5,76,79,82–86,150]. Central and peripheral anticholinergic stigmata frequently occur after overdose with chlorpromazine, clozapine, mesoridazine, olanzapine, and thioridazine [5,76,79,82–86].

In severe poisoning, high-grade coma with loss of most or all reflexes, apnea, hypotension, seizures, and a variety of cardiac conduction disturbances and arrhythmias may develop. Conduction disturbances include all degrees of AV block, bundle-branch and fascicular block, and nonspecific intraventricular conduction delay [31,46,48,49,54,58–61,147]. Bradyarrhythmias occur uncommonly and, when present, may signify impending respiratory arrest. Tachyarrhythmias include sinus and supraventricular tachycardias, supraventricular and ventricular premature beats, ventricular tachycardia and fibrillation, and TdP [5,31,45–49,57–61,151]. The latter arrhythmia typically occurs in the setting of QT-interval prolongation and has been described with amisulpride, droperidol, haloperidol, mesoridazine, pimozide, and thioridazine [152]. TdP has also been described when critically ill patients are given haloperidol for sedation. In one study, TdP occurred in 3.6% of such patients; the incidence was 64% in those given greater than 35 mg of haloperidol in less than 6 hours and 84% when given to those with a corrected QT (QTc) interval greater than 500 milliseconds [153]. TdP has been rarely associated with therapeutic (usually large) doses of droperidol [49,50,154]. Discovery of this association prompted the Federal Drug Administration to issue a "black box" warning to U.S. health care personnel for droperidol in 2001 [155]. Serious cardiovascular toxicity occurs more commonly when piperidine phenothiazines have been ingested [31]. In one study of 299 patients with neuroleptic overdose, thioridazine was associated with a significantly greater incidence of prolonged QRS, prolonged QTc, and arrhythmia as compared to other neuroleptics [31]. Electrocardiographic abnormalities or obvious cardiotoxicity should be evident within several hours of overdose. Newer agents alter cardiac conduction less frequently but are not entirely void of cardiotoxicity. Prolonged QRS and QT intervals and hypotension have been described after risperidone overdose, and ventricular tachycardia has occurred after remoxipride overdose [61]. The new drug approval application for sertindole was withdrawn in the United States due to dose-related prolongation of the QT interval that occurred during premarketing trials with the drug [53].

Although the overall seizure incidence is about 1% for patients that overdose on neuroleptics, the incidence is much greater following ingestion of chlorpromazine, clozapine, loxapine, mesoridazine, and thioridazine [5,30,31,54,76]. Occasionally, hypothermia or hyperthermia may be seen [156]. Pulmonary edema has been reported rarely as a complication of overdose with chlorpromazine, clozapine, haloperidol, and perphenazine [5,80,81]. Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction that rarely occurs after acute overdose. Acute overdose, however, may infrequently produce a clinical picture (i.e., the presence of hyperthermia, autonomic instability, neuromuscular hyperreactivity, and hypertonia) that could be misinterpreted as NMS [15]. Agents that produce anticholinergic effects (e.g., clozapine, mesoridazine, olanzapine, thioridazine) would be more likely to do this.

Loxapine poisoning results in an atypical clinical picture. Cardiovascular effects are mild or absent, but convulsions are common and often lead to rhabdomyolysis and subsequent renal failure [54,157].

Following overdose, toxic effects (e.g., CNS depression) begin within 1 to 2 hours, maximal severity is usually evident by 2 to 6 hours, and resolution usually occurs by 24 to 48 hours after ingestion. The presentation is the same regardless of age and whether the overdose is acute or chronic. Early deaths are due to respiratory arrest, arrhythmias, shock, or aspiration-associated respiratory failure. Later complications include cerebral and pulmonary edema, disseminated intravascular coagulation, rhabdomyolysis, myoglobinuric renal failure, and infection.

ADRs are characterized by abrupt onset, intermittent and repetitive nature, normal physical examination except for muscular findings, a history of recent neuroleptic use, and rapid response to anticholinergic drug therapy [98,103–105]. Muscle contractions may sometimes be sustained but usually last from seconds to minutes. They may be focal at the onset and then spread to contiguous muscles; occasionally, they are generalized [158]. Patients remain alert and oriented during these reactions.

Although dystonia may occur in any striated muscle, one of five areas is typically affected [98,103–105,159–161]. ADRs involving the muscles of the eye (oculogyric crisis) cause upward gazing, rotation of the eyes, and spasm of the lids. Those involving muscles of the tongue and jaw (buccolingual crisis) produce trismus, protrusion of the tongue, dysphagia, dysarthria, and facial grimacing. Contractions of muscles of the neck or back result in abnormal head positioning (torticollic reactions) or arching and twisting of the torso (opisthotonic posturing), respectively. When muscles of the abdominal wall are involved, patients present with abdominal wall pain and

spasm, bizarre gait patterns, kyphosis, and lordosis (tortipelvic and gait crises). Buccolingual and torticollic ADRs are the most common [103–105].

Although ADRs are rarely life threatening, those involving the tongue, jaw, neck, and chest can result in upper airway compromise and impaired respiratory mechanics [162,163]. Stridor can occur in those with buccolingual and torticollic reactions. Death from respiratory failure has been reported [162,164].

DIAGNOSTIC EVALUATION

The diagnosis of antipsychotic poisoning is made from a history of exposure, physical findings, and supporting evidence from electrocardiographic, laboratory, and other ancillary studies. A complete history should be obtained from the patient as well as the person(s) who found or brought the patient (to corroborate the patient's history). As with all drug ingestions, the name, quantity, and time of ingestion of the drug(s) should be determined. For patients who become toxic during chronic therapy, a recent medication or dose change or an illness may be responsible. Patients and family members should be specifically questioned about the possibility of antipsychotic exposure when signs of an EPS are present.

Physical examination should focus on the vital signs, respiratory function, and neurologic status. Physical findings that suggest neuroleptic poisoning include CNS and respiratory depression, sinus tachycardia, miosis, anticholinergic stigmata, orthostatic hypotension, and the presence of EPS. The patient should be examined for evidence of coexisting trauma. An initial rhythm strip and subsequent 12-lead electrocardiogram (ECG) should be evaluated. Arterial blood gas determinations and a chest radiograph should be ordered in patients with significant CNS depression. An abdominal radiograph showing radiopaque densities in the gastrointestinal (GI) tract may suggest butyrophenone or phenothiazine poisoning if the etiology of symptoms is unknown. The absence of this finding, however, does not rule out poisoning by these agents. Routine laboratory evaluation should include a complete blood cell count and electrolyte count and blood urea nitrogen, creatinine, and glucose tests. Measurements of serum acetaminophen and salicylate should be performed on all patients with intentional overdose. In patients with seizures, hyperthermia, and severe poisoning, laboratory evaluation should include urinalysis (routine and for myoglobin); creatinine phosphokinase, calcium, magnesium, and phosphate tests; and a coagulation profile. Women of childbearing age should have a pregnancy test performed.

Toxicologic analysis of the urine and serum by immunoassay and chromatography–mass spectrometry may be performed to confirm the identity of the offending agent and to rule out other ingestants [165]. Quantitative drug levels are not helpful in predicting clinical toxicity or guiding treatment [7,68,69,72]. Although neither sensitive nor specific, or readily available, the Forrest, Mason, and Phenistix (Ames Company, Inc., Elkhart, IN) colorimetric tests are rapid urine screens that may be positive with phenothiazine ingestions [166]. These tests, however, do not detect nonphenothiazine neuroleptic agents. Certain neuroleptics (e.g., chlorpromazine, mesoridazine, quetiapine, and thioridazine) will commonly produce false positive results for tricyclic antidepressants on most commercially available immunoassay screens used by hospitals to test for drugs of abuse [167].

Patients with ADRs should be questioned regarding current medications, previous ADRs, recreational drug use, and change in the dose of a neuroleptic or other medication associated with this syndrome. The diagnosis is made on the basis of history of drug exposure and the physical examination.

A complete blood cell count should be performed on patients who develop a fever or infection while taking clozapine or phenothiazines.

Agents that cause CNS and cardiovascular effects similar to those resulting from antipsychotic poisoning include antiarrhythmic, anticholinergic, anticonvulsant, antidepressant, antihistamine, opioid, other psychotropic agents (e.g., lithium, bupropion) and sedative–hypnotics, and skeletal muscle relaxants. It may be impossible to distinguish cyclic antidepressant or type IA antiarrhythmic agent poisoning from poisoning due to chlorpromazine, thioridazine, or mesoridazine without toxicologic analysis. CNS infection, cerebrovascular accident, occult head trauma, and metabolic abnormalities should also be considered in the differential diagnosis.

The differential diagnosis of an ADR includes primary dystonias, seizures, cerebrovascular accident, encephalitis, tetanus, hypocalcemia, drug intoxication (especially anticholinergic, anticonvulsant, and strychnine), hysterical conversion reactions, joint dislocations, meningitis, hypomagnesemia, torticollis, and alkalosis.

MANAGEMENT

All patients who are symptomatic after acute overdose should be observed until they are alert. Those with mild toxicity can often be managed in the emergency department or a similarly equipped observation unit. Those with protracted hypotension, significant CNS depression or agitation, seizures, acid-base disturbances, nonsinus arrhythmias, and cardiac conduction disturbances should be admitted to an intensive care unit. Patients with ECG abnormalities (e.g., prolonged QRS or QTc intervals) who are otherwise asymptomatic should be admitted to a cardiac monitored bed; such findings have been implicated in sudden death.

Treatment is primarily supportive. The tempo and sequence of interventions depend on the clinical severity. Advanced life support measures should be instituted as necessary, and underlying metabolic abnormalities corrected. All patients require cardiac and respiratory monitoring. Vital signs should be obtained frequently. Endotracheal intubation for airway protection or ventilatory support may be required. Patients with seizures or hyperthermia should have continuous (rectal probe) temperature monitoring. Those with altered mental status should receive supplemental oxygen and be given a diagnostic trial of naloxone (2 mg IV), dextrose (25 g IV), and thiamine (100 mg IV). Although reversal of CNS depression after naloxone administration has been reported [168], such a response is inconsistent with the pharmacology of neuroleptics and should not be expected.

Hypotension should be initially treated with Trendelenburg's position and several liters (10 to 40 mL per kg IV) of normal saline. α_1-adrenergic agonists (i.e., norepinephrine, phenylephrine) are first-line agents for treating refractory hypotension, particularly in patients who have been poisoned by antipsychotics with significant α_1-adrenergic blockade. Central venous, intra-arterial, and pulmonary artery pressure monitoring may be necessary for optimal management of patients who are hemodynamically unstable.

Sinus and supraventricular tachycardias rarely require specific treatment. If they are associated with hypotension, correction of this abnormality is often all that is necessary. Sodium bicarbonate (1 to 2 mEq per kg IV) may be effective and is strongly recommended for patients who have wide QRS complexes or ventricular tachyarrhythmias. Lidocaine (1 to 1.5 mg per kg IV) and electrical cardioversion are alternative treatments for patients with ventricular tachyarrhythmias, depending on hemodynamic stability. Type IA (i.e., disopyramide, quinidine, procainamide), type IC (i.e., propafenone), and type III (i.e., amiodarone) antiarrhythmic drugs are not recommended and are potentially dangerous; they may worsen cardiac conduction abnormalities [169]. TdP ventricular tachycardia should be treated with magnesium (50 to 100 mg per kg

IV over 1 hour); or an increase in heart rate (overdrive pacing) should be treated using isoproterenol or electricity [170–172]. Increasing the heart rate may shorten a prolonged QT interval and thus facilitate conversion of this arrhythmia. The blood pressure should be carefully monitored during isoproterenol administration, as it may cause or worsen hypotension. A search for and correction of hypokalemia, hypomagnesemia, and other electrolyte disturbances is requisite to the management of TdP. Bradyarrhythmias associated with hemodynamic compromise should be treated with atropine, epinephrine, dopamine, and isoproterenol according to current advanced cardiac life support protocols. Complete heart block may require temporary cardiac pacing.

Recent literature supports the antidotal use of intravenous fat emulsions (IFE) for severe central nervous system or cardiovascular toxicity from highly lipophilic drugs [173]. IFE infusions may create a "lipid sink" whereby lipophilic drugs are sequestered in a newly created intravascular lipid compartment, thereby reducing tissue binding. Alternatively, IFE infusions may restore myocardial function by providing exogenous fatty acid substrate or by increasing intracellular calcium for myocyte function [173]. In a rabbit model of chlorpromazine toxicity, IFE treatment decreased free drug available for tissue toxicity and increased survival in poisoned animals [174]. In human case reports, IFE administration has been temporally associated with attenuation of QTc prolongation and CNS depression from quetiapine overdose [175,176]. The overwhelming majority of antipsychotic-overdose patients do well with good supportive care and would not necessitate IFE infusion therapy. ILE treatment, however, should be strongly considered and is recommended for patients with severe and refractory cardiovascular or CNS toxicity from antipsychotic drugs. IFE is commonly administered an IV bolus followed by a 3 to 24 hour continuous infusion. A reasonable dosing algorithm for both adults and children is a 1 to 2 mL per kg IV bolus of 20% IFE over 1 minute followed by 0.25 to 0.5 mL per kg per minute continuous IV infusion (total dose 2 g per kg per day IFE) [173].

Seizures are often self-limited and may not require specific treatment. If prolonged or recurrent, seizures should be treated with incremental doses of diazepam or lorazepam (initial dose, 0.05 to 0.10 mg per kg IV). A short-acting barbiturate (e.g., amobarbital, 10 to 15 mg per kg IV at a maximal rate of 100 mg per minute) or a long-acting one (e.g., phenobarbital, 20 mg per kg IV at a maximal rate of 30 mg per minute) may sometimes be necessary. The effectiveness of phenytoin is not established for neuroleptic-associated seizures. Refractory convulsions, as seen in loxapine poisoning [54,157], may require the use of a paralyzing agent to prevent complications such as hyperthermia and rhabdomyolysis. A nondepolarizing neuromuscular blocker, such as pancuronium (0.06 to 0.10 mg per kg IV) or vecuronium (0.08 to 0.10 mg per kg IV) is recommended over succinylcholine. Continued treatment of seizures, as indicated by electroencephalogram monitoring, is necessary during therapeutic paralysis. Diuresis and alkalinization of urine may be useful in preventing myoglobinuric renal failure for patients with rhabdomyolysis (see Chapter 73).

Physostigmine may be used safely and effectively in poisoned patients who have significant peripheral or central anticholinergic stigmata (i.e., agitated delirium) and normal PR and QRS intervals on ECG (see Chapter 121) [99]. Its use has been described with chlorpromazine, clozapine, olanzapine, and thioridazine poisoning [83,85,86]. Physostigmine should be given slowly intravenously (0.02 mg per kg in children or 2 mg in adults) over 3 minutes. Alternatively, agitated delirium from the anticholinergic syndrome may be treated with benzodiazepines.

After stabilization, GI decontamination should be performed for patients with acute ingestions. Oral activated charcoal (1 g per kg) with or without a cathartic is the preferred method for the majority of patients. Although gastric lavage may benefit comatose patients who present within 1 hour of drug ingestion, it is not routinely recommended for neuroleptic overdose for which the mortality rate is very low [177]. If performed, gastric lavage should always be followed with activated charcoal administration. Because of decreased GI tract motility resulting from poisoning, decontamination (activated charcoal administration) may be of benefit many hours after overdose.

Although clinical improvement was reported during combined hemodialysis and charcoal hemoperfusion [178], the effect was transient, and measures to enhance the elimination of neuroleptic agents, such as diuresis, dialysis, and hemoperfusion, have not been shown to be pharmacokinetically effective [179,180]. Repeated oral doses of activated charcoal are of potential but unproved benefit. Use of multidose charcoal is not recommended and potentially harmful for patients who have developed an ileus.

The vast majority of patients with neuroleptic poisoning recover completely within several hours to several days, depending on severity. Patients with intentional overdosage require psychiatric evaluation before discharge.

Patients with respiratory distress secondary to ADRs should be given supplemental oxygen. Those with buccolingual and torticollic crises should be given nothing by mouth, because doing so could precipitate choking. Because ADRs rarely result from an overdose, GI tract decontamination is usually not indicated and may, in fact, be hazardous because of the potential for airway complications.

Administration of an anticholinergic agent readily reverses ADRs, presumably by restoring the balance between cholinergic and dopaminergic pathways in the basal ganglia [98]. Benztropine mesylate, 1 to 2 mg, or diphenhydramine, 50 to 100 mg, given intravenously over 1 to 2 minutes, can be used. Reversal of signs and symptoms usually occurs within a few minutes. In some cases, a second dose is needed for complete resolution. Benztropine appears to be more effective and is less likely to cause sedation and hypotension than diphenhydramine and is the preferred agent in adults [105,181]. Although benztropine is contraindicated in children younger than 3 years of age because of its anticholinergic effects [182], this is precisely the desired effect, and its administration in small doses (e.g., 0.25 to 0.50 mg) is appropriate in this situation. As an alternative, diphenhydramine (1 mg per kg IV) can be used. Benztropine and diphenhydramine can also be given intramuscularly, but it may take 30 to 90 minutes for the ADR to resolve when this route is used. Cases resistant to anticholinergic agents may respond to diazepam (0.1 mg per kg IV) or lorazepam (0.05 to 0.10 mg per kg IV).

Subsequent therapy with an oral anticholinergic agent should be continued for 48 to 72 hours. Without such therapy, the ADR may recur because it may take several days to eliminate completely the agent that caused it and the duration of action of drugs used to treat it is much shorter. In addition to benztropine and diphenhydramine, biperiden (2 mg 1 to 3 times a day), trihexyphenidyl (2 mg twice per day), or amantadine (100 to 200 mg twice per day) can be used for oral therapy. For reasons already noted, benztropine (1 to 2 mg twice per day) is the preferred agent for adults. Children younger than 3 years can be given diphenhydramine (1 mg per kg orally three or four times per day). Although patients who have had an ADR are at increased risk for future ADRs, those requiring continued antipsychotic therapy can usually continue or resume taking the offending agent provided they are also maintained on anticholinergic therapy. As an alternative, they can be switched to atypical antipsychotic with less dopaminergic-blocking activity.

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CHAPTER 125 ■ BETA-BLOCKER POISONING

SHAN YIN AND JAVIER C. WAKSMAN

Since 1958, when dichloroisoprenaline, the first β-adrenergic blocker, was synthesized, more than a dozen beta-blockers have been introduced into the international pharmaceutical market. Originally developed for the treatment of angina pectoris and dysrhythmias, beta-blockers are now used in a wide variety of disorders. Intoxication may result from oral, parenteral, and even ophthalmic use [1].

PHARMACOLOGY

Beta-blockers act by competitively inhibiting the binding of epinephrine and norepinephrine to β-adrenergic neuroreceptors in the heart (β_1), blood vessels, bronchioles (β_2), and other organs (Table 125.1). Binding to the β receptor (G-protein–coupled receptor) activates phosphodiesterase and increases cytoplasmic cyclic adenosine monophosphate (cAMP). This in turn leads to modification of cellular processes and changes in ionic channel conductance. By reducing the activity of β receptors, the production of cAMP is decreased and β effect is diminished [2].

Beta-blockers are usually rapidly absorbed after oral administration. The beta-blocker dose required to produce a toxic effect is variable, depending on the sympathetic tone and metabolic capacity of the person and the pharmacologic properties of the particular beta-blocker [2]. The first signs of toxicity may appear 20 minutes after ingestion, with peak effects typically occurring 1 to 2 hours after an immediate-release preparation overdose. Absorption of modified-release formulations may be erratic after an overdose, however, and clinical

TABLE 125.1

DISTRIBUTION AND FUNCTION OF β-RECEPTORS

Receptor subtype	Location	Response to stimulation
β_1	Eye	Aqueous humor production
	Heart	Increased automaticity, conduction velocity, contractility, and refractory period
β_2	Kidney	Renin production
	Blood vessels	Smooth muscle contraction
	Bronchioles	Smooth muscle contraction
	Fat	Lipolysis
	Liver	Gluconeogenesis, glycogenolysis
	Pancreas	Insulin release
	Skeletal muscle	Increased tone, potassium uptake
	Uterus	Smooth muscle relaxation

toxicity may be significantly delayed. The duration of toxicity may be several days [2].

The pharmacologic and pharmacokinetic properties of beta-blockers are variable (Table 125.2). Cardioselectivity tends to be lost at high doses, and membrane-stabilizing effects, which are minimal at therapeutic doses, assume a more important role [2]. Membrane dysfunction may account for many of the central nervous system (CNS) and myocardial depressant effects in patients poisoned by membrane-active drugs such as propranolol. The half-life may be significantly prolonged in patients with decreased hepatic and renal perfusion [2]. Intrinsic heart, kidney, and liver disease as well as the concomitant use of drugs with similar activity increase the risk of toxicity.

CLINICAL TOXICITY

The major manifestations relate to the cardiovascular system and CNS. Respiratory, peripheral vascular, and metabolic (hypoglycemic and hyperkalemic) effects have been infrequently reported [2,3].

Patients with severe poisoning frequently present with hypotension and bradycardia. Tachycardia and hypertension have been reported with agents possessing intrinsic sympathomimetic activity, however, particularly pindolol [2]. Congestive heart failure and pulmonary edema have infrequently been reported and mainly occur in patients with underlying heart disease [4]. Electrocardiographic manifestations may include prolonged PR interval, intraventricular conduction delay, progressive atrioventricular heart block, nonspecific ST-segment and T-wave changes, early repolarization, prolonged corrected QT (QTc) interval, and asystole [5–7]. Sotalol poisoning may result in ventricular tachycardia, torsade de pointes, ventricular fibrillation, and multifocal ventricular extrasystoles [8,9]. Labetalol, which also has mild β-receptor–blocking properties, may cause profound hypotension, possibly from decreased peripheral resistance.

Depression in the level of consciousness, ranging from drowsiness to coma with seizures, is another common feature of beta-blocker poisoning. Significant CNS depression has been reported in the absence of cardiovascular compromise [2] or hypoglycemia and may be due to direct membrane effects [10]. Cerebral hypoperfusion, hypoxia, and metabolic or respiratory acidosis frequently contribute to CNS toxicity. Beta-blockers with high lipid solubility (e.g., propranolol, penbutolol, metoprolol) appear more likely to cause CNS effects than those with low lipid solubility (e.g., atenolol) [11,12].

Bronchospasm is a relatively rare consequence of beta-blocker poisoning and usually occurs more frequently in patients with preexisting reactive airway disease. In most instances, respiratory depression appears to be secondary to a CNS effect [13–16].

Although it does occur, hypoglycemia is not a common complication of beta-blocker poisoning [17]. It appears to be more common in diabetics, children, and uremic patients and it is the consequence of impaired glycogenolysis and hepatic gluconeogenesis [18]. A blunted tachycardic response to hypoglycemia may occur in patients with beta-blocker toxicity, although other symptoms of hypoglycemia appear unaffected.

Oliguric renal failure has been reported as a complication of labetalol poisoning [19]. Mesenteric ischemia and subsequent cardiovascular collapse have occurred after propranolol overdose [20].

Sudden discontinuation of long-term beta-blocker therapy may precipitate angina pectoris and myocardial infarction. This is the result of the "beta-blocker withdrawal phenomenon," explained by the theory that long-term beta-blocker therapy not only diminishes receptor occupancy by catecholamines but also increases the number of receptors sensitive to adrenergic stimulation. When beta-blockers are suddenly withdrawn, the increased pool of sensitive receptors responds more readily to the stimulation of circulating catecholamines [17].

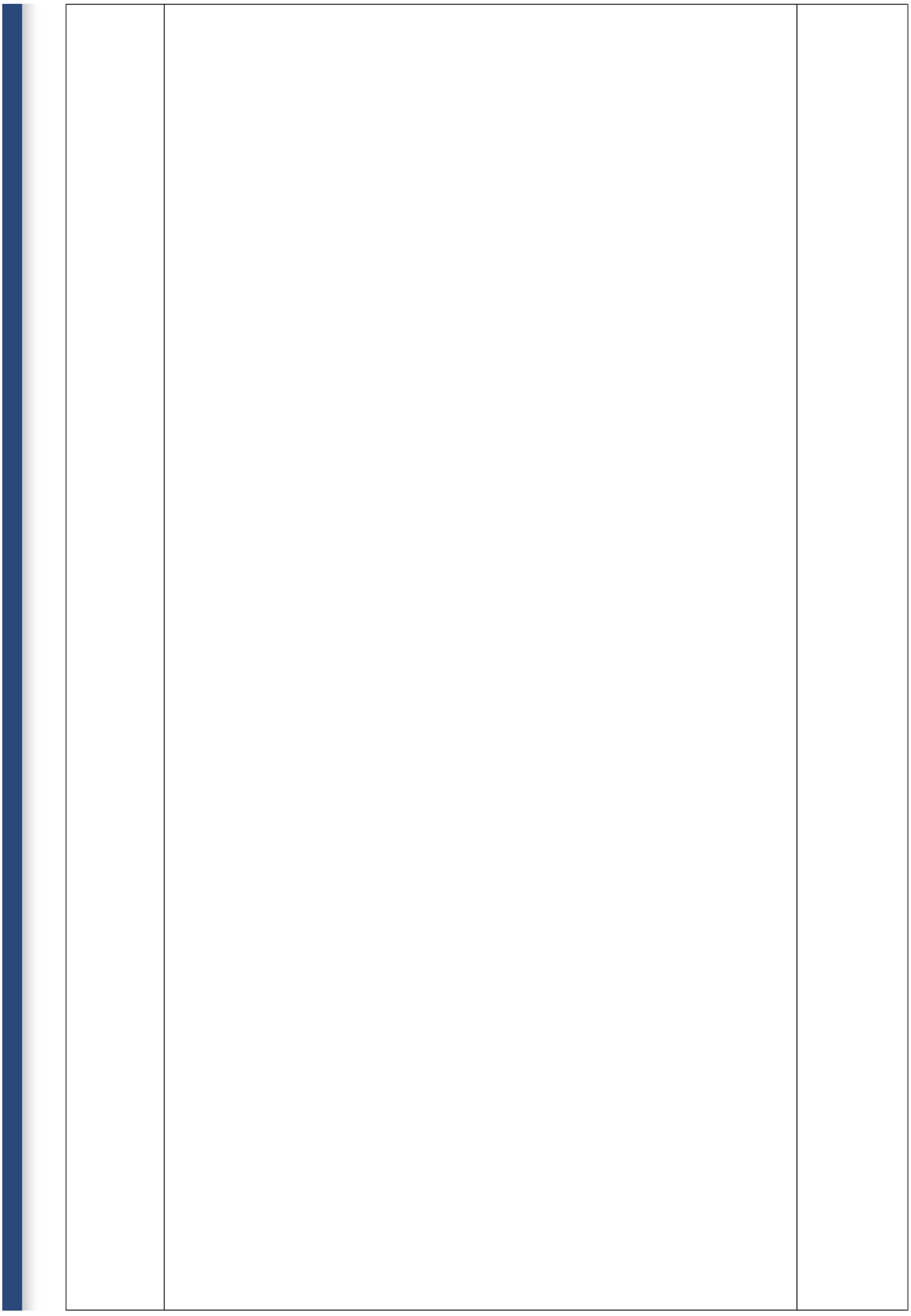
DIAGNOSTIC EVALUATION

The history should include the time, amount, and formulation of drugs ingested; the circumstances involved; time of onset and nature of any symptoms; and treatments rendered before arrival, as well as underlying health problems. Beta-blocker poisoning may be difficult to recognize, especially when multiple drugs have been ingested [2]. Beta-blocker poisoning should be suspected in a patient in whom hypotension or seizures suddenly develop or who has bradycardia resistant to the usual doses of chronotropic drugs [21]. Evaluation of patients with suspected beta-blocker poisoning should begin with a complete set of vital signs, continuous cardiac rhythm monitoring, and a 12-lead electrocardiogram. Physical examination should focus on the cardiovascular, pulmonary, and neurologic systems. Vital signs and physical examination should be frequently repeated.

Serum drug levels may help confirm the diagnosis but are rarely available quickly enough to be clinically useful. In addition, differences in individual patient metabolism and sympathetic tone may make interpretation of blood levels difficult [2,3]. A serum and urine specimen can be saved for later analysis in forensic cases. Continuous cardiac rhythm monitoring, interpretation of 12-lead electrocardiograms, and measurement of oxygen saturation should be routine. Laboratory evaluation of symptomatic patients should include electrolytes, blood urea nitrogen, creatinine, bicarbonate, and glucose. Arterial blood gas and a chest film should be obtained as clinically indicated. Serum acetaminophen and aspirin levels should be obtained in patients with suicidal ideation.

The differential diagnosis of beta-blocker toxicity includes antidysrhythmic drugs, calcium channel blockers, cholinergic agents, clonidine, digitalis, narcotics, sedative hypnotics, and tricyclic antidepressants. Anaphylactic, cardiogenic, hypovolemic, and septic shock should also be considered.

The prognosis associated with beta-blocker intoxication is generally positive. A review of two regional poison control centers [22] found that 15% of patients developed cardiac toxicity, and only 1.4% died. The only factor associated with increased



morbidity was coingestion of cardioactive drugs such as calcium channel blockers, cyclic antidepressants, and neuroleptics [22].

MANAGEMENT

Treatment is primarily supportive. This may include prompt endotracheal intubation and mechanical ventilation and management of life-threatening bradydysrhythmias, hypotension, bronchospasm, and seizures. These attempts should precede any measures (as described later) used to prevent or reduce drug absorption. A bedside glucose measure or, alternatively, an intravenous bolus of glucose (50 mL of $D_{50}W$ in adults; 4 mL per kg of $D_{25}W$ in children) as well as naloxone (2 mg in adults and children) should be given to patients with altered mental status (Fig. 125.1).

Activated charcoal is the preferred methods for gastrointestinal decontamination [14]. Gastric lavage has not been shown to improve outcome after poisoning and should not be used routinely, but considered for recent life-threatening ingestions in patients who have not already vomited [23]. Lavage may cause bradycardia from vagal effects. Thus, atropine should be given prior to initiation, and lavage should be withheld in patients with existing bradycardia and conduction abnormalities. Whole-bowel irrigation with polyethylene glycol (Golytely^{TM}) at a rate of 2 L per hour until the rectal effluent is clear may be considered for gastrointestinal decontamination in modified-release preparation overdoses.

Hypotension should be first treated with judicious intravenous crystalloid fluids. Because hypotension seldom responds solely to this treatment and because administration of high volumes (greater than 2 L) of intravenous fluids may pose a risk to develop pulmonary edema, the prompt use of inotropic drugs such as dopamine, dobutamine, epinephrine, norepinephrine, and phenylephrine is usually required [24]. Bradycardia from β-adrenergic antagonist poisoning seldom responds to atropine.

Calcium

The goal of calcium therapy is to increase extracellular calcium concentrations thus increasing calcium influx through any unblocked calcium channels. Calcium has demonstrated effectiveness in animal models [25] and improvement reported in human cases [26]. However, responses are variable and often short-lived, and patients with significant toxicity usually fail to improve with calcium alone. Conduction disturbances, contractility, and blood pressure, may be improved, but generally there is no increase in heart rate. Optimum dosing has yet to be established.

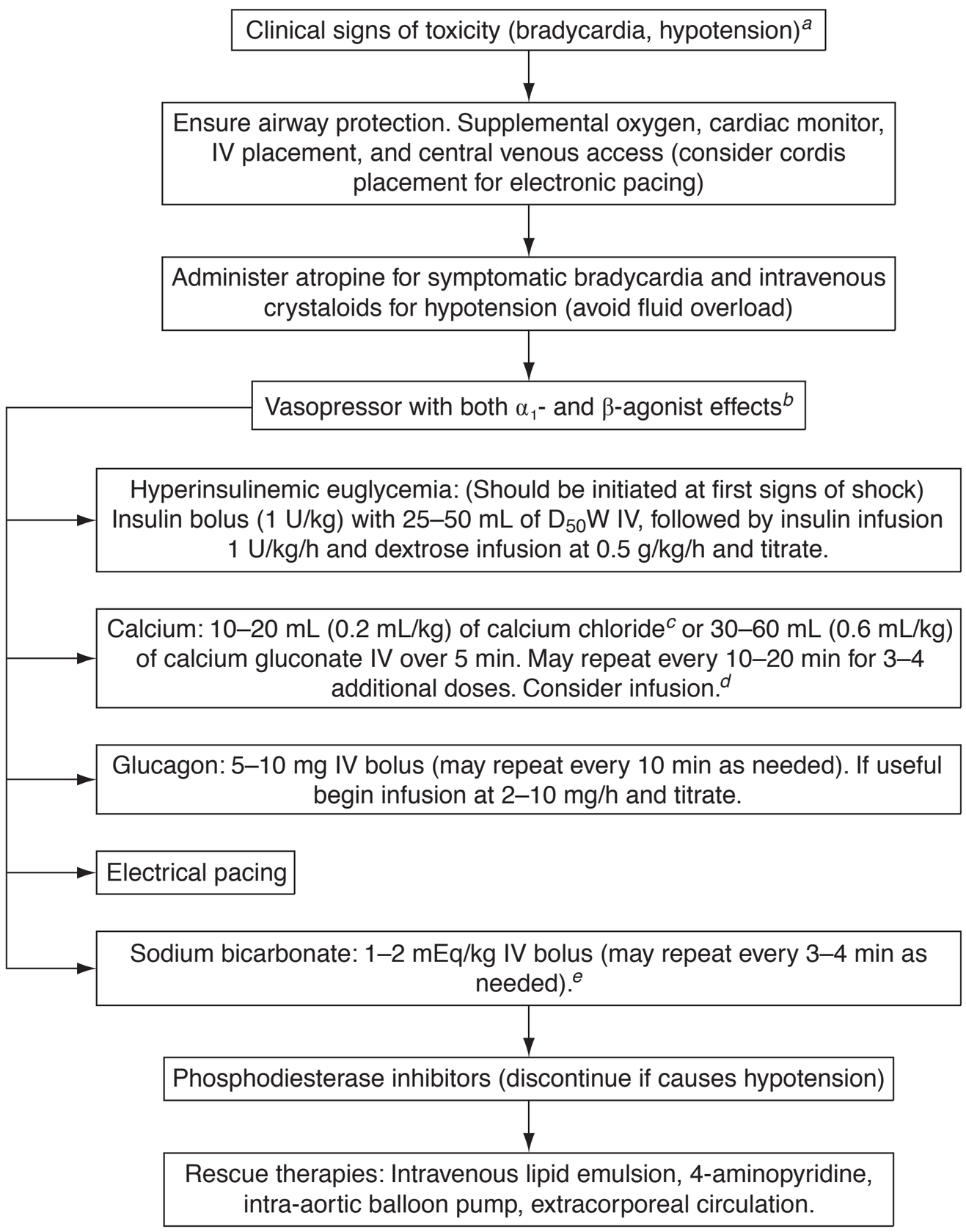


FIGURE 125.1. Suggested algorithm for treatment of beta-blocker poisoning. [a]Patients with significant toxicity will often require multiple therapies and the initiation of these simultaneously. In less severely poisoned patients, therapies can be added sequentially depending on clinical response. Decontaminate on a case-by-case basis, but preservation of vital signs takes precedence over decontamination. [b]May need multiple pressors at very high doses. [c]Administer calcium chloride via a central venous catheter. [d]Calcium infusion: 0.4 mL/kg/h of calcium chloride or 1.2 mL/kg/h of calcium gluconate. May allow higher doses and permissive hypercalcemia depending on response. [e]Administer sodium bicarbonate for wide complex conduction defects caused by beta-blocking agents with membrane stabilizing activity.

Calcium chloride compared to calcium gluconate contains three times the amount of elemental calcium on a milliequivalent basis (10% calcium chloride: 272 mg elemental calcium or 13.6 mEq per 1 g ampule; 10% calcium gluconate: 90 mg elemental calcium or 4.5 mEq per 1 g ampule). However, it is recommended to only give calcium chloride via a central venous catheter. Calcium gluconate can be given via a peripheral line.

Optimum calcium dosing is not well established. Initial doses are generally given as boluses (10 to 20 mL of 10% calcium chloride or 30 to 60 mL of 10% calcium gluconate). Additional boluses may be given every 10 to 20 minutes. Boluses should be given over a 5-minute period in conjunction with cardiac monitoring as rapid infusions have resulted in hypotension, atrioventricular dissociation, and ventricular fibrillation. The effects of boluses may be transient, and a constant infusion required. Infusions can be started at 0.4 mL per kg per hour for calcium chloride and 1.2 mL per kg per hour for calcium gluconate and titrated to effect. Additional boluses can be given as needed. Calcium levels should be monitored. Raising serum ionized calcium to 2 to 3 mEq per L improves canine cardiac performance in verapamil poisoning, and is a reasonable goal to attain. It may be necessary to continue therapy despite high serum calcium levels if the patient is only responding to calcium administration. Hypercalcemia can lead to renal failure and limb or mesenteric ischemia. It is recommended to stop calcium infusions if no beneficial effect is observed.

Glucagon

Although there are no controlled trials of glucagon for beta-blocker overdose in humans, glucagon has served as an effective agent for reversing hypotension and bradycardia in multiple case reports [14,27–29]. Glucagon has a half-life of 20 minutes, so a continuous intravenous infusion of 1 to 10 mg per hour is recommended after an initial bolus of 3 to 10 mg for adults. In children, an initial intravenous dose of 0.05 mg per kg should be followed by a continuous infusion of 0.07 mg per kg per hour [2,3,27]. This dose is titrated to patient response, and large total doses may be required. The dose should be tapered once the patient's clinical condition improves. The mechanism by which glucagon produces a positive inotropic and chronotropic effect on the heart is believed to be activation of the adenyl cyclase pathway, which converts adenosine triphosphate to cAMP through an independent receptor, changing membrane ion conductivity, altering calcium influx, and augmenting contractility even in the presence of complete β-adrenergic blockade [28]. It is recommended that glucagon be reconstituted in a solution of 5% dextrose in water or in preservative-free saline, rather than the diluent provided by the manufacturer, as the latter contains phenol that might be toxic in the large doses often needed to treat beta-blocker toxicity [27,30]. Severe phenol toxicity is usually manifested as chemical burns, lethargy, coma, cardiac dysrhythmias, and death [31]. Non–phenol-containing, high-dose glucagon preparations are now available [32].

Phosphodiesterase Inhibitors

The simultaneous use of multiple agents may be effective when a single agent fails. Although theoretically promising, phosphodiesterase inhibitors such as amrinone and milrinone, which inhibit the breakdown of cAMP to AMP, have not proven to be superior to glucagon in reversing the hemodynamic effects of beta-blocker overdose in a canine model [33,34]. Other studies using dogs have shown no additional benefit of combining a phosphodiesterase inhibitor with glucagon [35,36]. It has been suggested that phosphodiesterase inhibitors might be used in cases of beta-blocker poisoning when adequate doses of glucagon are not available [33]. The phosphodiesterase inhibitor enoximone has been successfully used in cases of beta-blocker overdoses [37].

Sodium Bicarbonate

A number of beta-blockers (propranolol, carvedilol, pindolol, and acebutolol) also affect cardiac sodium channels producing membrane stabilizing effects which may result in quinidine-like dysrhythmias (e.g., wide QRS complexes). This effect may respond to intravenous boluses of sodium bicarbonate albeit in a canine model; sodium bicarbonate was ineffective in treating propranolol toxicity that resulted in bradycardia, hypotension, and wide QRS intervals [38]. In a case report, sodium bicarbonate appeared to reverse QRS widening following an acebutolol overdose [39]. The recommended dose is 1 to 2 mEq per kg given as a rapid infusion over several minutes.

Hyperinsulin–Euglycemia Treatment

High-dose insulin while maintaining euglycemia has been proposed as an antidote for beta-blocker poisoning [40]. Insulin is an inotropic agent which may enhance response to catecholamines and reverse metabolic acidosis. Although results in animals remain encouraging [41–43], further studies are needed in humans. Several case reports described successful insulin–euglycemia therapy for calcium channel blocker toxicity [44] (one patient also ingested a beta-blocker). Therefore, this treatment should be considered an option in patients with refractory beta-blocker toxicity as both classes bear similarities in the clinical manifestation and mechanism of toxicity [45]. The recommended doses are 0.5 to 1.0 IU per kg per hour [40]. A second intravenous infusion of $D_{10}W$ or $D_{25}W$ containing potassium chloride should be simultaneously administered to the insulin infusion at a rate sufficient to maintain the serum glucose and potassium concentrations in the normal range.

Vasopressin

The use of vasopressin in beta-blocker toxicity has been suggested. In one animal trial which compared vasopressin with glucagon in the treatment of beta-blocker toxicity, vasopressin was neither found to increase survival nor had a significant effect on any of the cardiac parameters tested relative to glucagon [46]. High-dose insulin treatment also improved survival when compared to vasopressin with epinephrine in a swine model [43].

Lipid Emulsion

The use of lipid emulsion has been suggested in the treatment of the cardiotoxic effects of local anesthetics. Various animal models of bupivacaine toxicity have demonstrated faster return of spontaneous circulation following treatment with lipid emulsion therapy [47,48] as well as improved cardiodynamic parameters when compared with epinephrine [49]. However, a pig model did not show any improvement in survival when compared to saline controls [50]. Positive outcomes with the use of lipid emulsion were described in human case reports of bupivacaine [51–53], bupropion and lamotrigine [54], and quetiapine and sertraline overdoses [55]. Lipid emulsion was also investigated for the treatment of beta-blockers toxicity; however, there is currently no experience in humans. In a rabbit model, lipid emulsion successfully improved hypotension

induced by propranolol when compared with placebo [56]. In a separate study on rats, pretreatment with lipid emulsion resulted in a significant reduction in QRS duration and a non-significant improvement in bradycardia induced by propranolol when compared to placebo [57]. The mechanism of how lipid emulsion may be beneficial is not completely understood. The possible explanations include the creation of lipid sink for fat-soluble drugs, augmentation of cardiac energy substrates, or the improvement of myocardial function by increasing intracellular calcium [58]. No standard dosing regimen exists. However, a loading dose of 1.5 mL per kg administered over 1 minute, repeated one or two times every 3 to 5 minutes as needed is often used. If hemodynamic improvement is noted, the loading dose should be followed by a continuous infusion at a rate of 0.25 to 0.5 mL per kg per minute. Further information can be found at www.lipidrescue.org.

Extracorporeal Removal

Although the efficacy of hemodialysis in acute beta-blocker poisoning has not been studied in controlled clinical trials, it is theoretically useful in removing beta-blockers that have a low volume of distribution, are not significantly protein bound, and are hydrophilic. This would include acebutolol, atenolol, nadolol, sotalol, and timolol. Hemodialysis appeared to be clinically useful in a number of case reports involving atenolol, acebutolol, sotalol, and nadolol poisoning [59,60] and in cases of refractory torsade de pointes due to sotalol [61,62]. Charcoal hemoperfusion has also been suggested as an adjunctive therapy in patients severely poisoned with beta-blockers, although experience is limited [63]. Continuous venovenous hemodiafiltration was also successfully used in the treatment of a combined atenolol/nifedipine overdose [64]. The molecular adsorbent recirculating system (MARS) is a blood purification system that may be effective in removing protein bound toxins. There are case reports describing its successful use in theophylline [65] and phenytoin [66] MARS may theoretically be helpful in removing highly protein bound beta-blockers such as propranolol and carvedilol.

Other Interventions

Transient blood pressure elevations caused by pindolol usually require no specific treatment. Short-acting agents such as nitroprusside should be used if marked blood pressure elevation occurs, especially if it is accompanied by organ ischemia. Ventricular dysrhythmias induced by sotalol have been treated with lidocaine, isoproterenol, magnesium, and cardioversion defibrillation [6]. Electrical cardiac pacing may be needed if bradycardia, hypotension, and heart block fail to respond to pharmacologic therapy [2], or if ventricular tachydysrhythmias associated with a prolonged QTc interval are difficult to control [6]. In severe overdoses, a pacemaker may not capture. If capture occurs, the increased heart rate may not increase blood pressure. Heart rates greater than 90 to 100 beats per minute significantly decrease diastolic filling time and may adversely affect inotropy. Intra-aortic balloon pump counterpulsation [32] and extracorporeal circulation [67,68] have been successfully used for cardiovascular support.

Patients with beta-blocker overdose who have abnormal vital signs, altered mental status, or dysrhythmias on presentation should be admitted to an intensive care unit. If vital signs can be supported, complete recovery should be expected within 24 to 48 hours. Patients may be discharged after at least 6 hours of emergency department observation if they have ingested an immediate-release product, present with mild to absent toxicity and remain or become asymptomatic, have normal vital signs on discharge, and have received activated charcoal. These patients should be referred for psychiatric evaluation in the event of an intentional overdose or discharged in the care of a reliable observer after an accidental overdose. Any other symptoms mandate longer observation or admission. Because of the potential for delayed toxicity, prolonged observation is recommended after modified-release preparation overdose.

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CHAPTER 126 ■ CALCIUM CHANNEL ANTAGONIST POISONING

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INTRODUCTION

Calcium channel antagonists (CCA) effectively treat a variety of medical conditions. Yet, accidental and intentional overdoses of theses agents can be life threatening. CCAs consistently top the list of cardiovascular medications with the greatest proportion of deaths per exposure [1–3]. Severely poisoned patients demonstrate cardiovascular collapse as well as metabolic derangements similar to diabetic acidosis. Cardiovascular instability is often refractory to typical cardiotonic therapies and medication doses. There is no antidote for CCAs, and no controlled clinical studies to guide therapy. Treatment recommendations are therefore based on case series, case reports, animal

studies, and extrapolation. Simultaneous use of multiple therapies is often required and should be tailored to the patient's cardiovascular and metabolic responses. Overall goals of treatment are to provide supportive care, optimize cardiovascular and metabolic function, and decrease drug absorption. If vital signs can be supported until the drug is metabolized or eliminated, most patients will survive without sequelae.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Available CCAs antagonize calcium influx through L-type voltage sensitive channels [4], a specific type of calcium channel found in the heart, vascular smooth muscle, and pancreatic β-islet cells. Multiple physiologic functions are dependent on this calcium influx.

In the cardiovascular system, calcium influx through L-type channels is responsible for the spontaneous pacemaker activity of the sinoatrial (SA) node and depolarization of the atrioventricular (AV) node [4,5]. Other myocardial cells rely on sodium influx for initial depolarization [5,6], but calcium entry via L-type channels contributes to the plateau phase of their action potential [5,7]. Calcium entering during the plateau phase signals the release of additional calcium from the sarcoplasmic reticulum into the cytosol, allowing contraction to occur [5,8,9]. The magnitude and duration of sarcoplasmic calcium release and myocardial contraction is proportional to the magnitude and duration of calcium entry via L-type channels [8]. Vascular smooth muscle tone is also maintained by a similar mechanism [8]. Thus, therapeutic clinical effects of CCAs arise from blockade of L-type channels resulting in decreased cytosolic calcium levels. Depending on the class of CCA administered (see Pharmacology section), the clinical result is depression of SA node automaticity, AV node conduction, myocardial contractility, and vasodilation. The pathophysiologic effects of CCA overdose are essentially an exaggeration of pharmacologic effects that lead to cardiovascular shock. In canines, shock ensues despite a 14-fold or greater increase in endogenous catecholamine concentrations [10–12].

In addition to cardiovascular effects, CCA poisoning also produces a diabetogenic effect of hyperglycemia and acidosis. Insulin secretion is dependent on calcium influx into pancreatic β-islet cells. Although generally not a concern at therapeutic doses, CCBs decrease insulin secretion [13–16]. In canine models of verapamil-induced shock, systemic insulin levels fail to increase in response to an intact glucogenic response and hyperglycemia [10,12,17]. Experimentally, verapamil toxicity also produces systemic [12,18] and myocardial [10] resistance to insulin-mediated carbohydrate uptake. The cause of this resistance may be multifactorial involving decreased substrate delivery from poor perfusion, interference with calcium-dependent cellular insulin responsiveness and glucose uptake, and inhibition of calcium-stimulated mitochondrial dehydrogenases (i.e., pyruvate dehydrogenase) and glucose catabolism [12]. More recent evidence suggests CCAs interfere with cellular signaling, specifically recruitment of glucose transporter proteins (GLUTs) from the intracellular space to cell membranes [19]. These GLUTs are responsible for normal cellular uptake of glucose.

Verapamil toxicity also produces a state of hyperlacticacidemia due to a combination of tissue hypoperfusion and probably a defect in carbohydrate metabolism [12]. In stressed states such as CCA toxicity, the heart switches from preferentially using free fatty acids to carbohydrates (glucose and lactate) for energy production [10,11,17]. Although there is an abundance of circulating carbohydrates (e.g., glucose and lactate), they are essentially unavailable for use because of insulin resistance and decreased insulin availability.

In essence, CCAs decrease cytosolic calcium levels resulting in desirable cardiovascular effects at therapeutic doses, and at toxic doses an exaggeration of those effects. Additionally, toxicity produces a vicious cycle where the myocardium is preferentially metabolizing carbohydrates yet carbohydrate utilization is hindered by impaired insulin release and insulin resistance.

PHARMACOLOGY

In the United States, available CCAs fall into one of three classes: phenylalkylamine (verapamil), benzothiazepine (diltiazem), and dihydropyridines (nifedipine and all other agents). At therapeutic doses, each class has differing affinities for myocardial tissues and vascular smooth muscle. Verapamil and diltiazem are potent inhibitors SA node automaticity, AV node conduction, myocardial contractility, and cause modest vasodilation [20,21]. Verapamil affects the SA node, contractility, and vasodilation more than diltiazem [20,21]. This is probably why verapamil generally causes more deaths than other CCAs [1–3]. Dihydropyridines are far more selective for vascular smooth muscle, and at therapeutic doses have very little effect on cardiac pacemaker cells or contractility [9,20,21]. In significant poisoning this selectivity is lost however.

Pharmacologic properties of CCAs make extracorporeal removal of limited or no value as demonstrated in several cases [22–24], although plasmapheresis was believed to be beneficial in several cases [25–27]. Therapeutic half-lives of CCBs are variable, but in overdose can be prolonged [22,28–31]. The duration of toxicity in most cases is less than 24 hours, but has been reported to last 48 hours with sustained release (SR) verapamil [32] and for more than 5 days with amlodipine [33].

Verapamil, diltiazem, nifedipine, and several of the newer dihydropyridines are available in both immediate release (IR) and SR formulations. This information becomes important when considering how long to observe asymptomatic patients after an overdose. Immediate-release preparations produce signs or symptoms of toxicity within 6 hours of ingestion [34] whereas toxicity with SR products may be delayed 6 to 12 hours [34–37] or rarely longer [38]. Amlodipine, a dihydropyridine, has unique pharmacokinetics however. It is not a sustained release product, but has a late onset of peak effect and long half-life allowing for delayed and prolonged toxicity.

There is no accurate definition of a toxic dose, and patients have demonstrated significantly different effects at similar doses. Unintentional overdoses are common, but uncommonly result in significant effect. However, several adult patients have developed toxicity and death at doses less than maximum recommended daily doses [39]. Factors that could have contributed to this are advanced age, underlying medical conditions, additional medications, and chewing and swallowing SR preparations—essentially changing the pharmacokinetics into an IR formulation [39]. In general, the most significant poisonings are large intentional ingestions, but patients with significant underlying medical diseases, or advanced age can have significant effects at lower doses.

CLINICAL MANIFESTATIONS

Cardiovascular effects are the primary manifestation of CCA poisoning. Alterations in mental status without significant hypotension should not be attributed to CCA ingestion. Minimally intoxicated patients, or those who present soon after ingestion, may demonstrate no signs of toxicity. All CCAs can cause hypotension in overdose. However, the cause of the hypotension is typically an extension of the drugs' therapeutic effects. (i.e., dihydropyridines causing significant vasodilation with reflex tachycardia where verapamil and diltiazem slow

SA and AV node conduction, decrease contractility, and cause vasodilation) Thus, in overdose normal sinus rhythm or reflex tachycardia is commonly seen with nifedipine [34,37,40], where sinus bradycardia, AV nodal blocks, and junctional rhythm are common with verapamil and diltiazem [34,37,41]. This selectivity may be lost in large overdoses so that dihydropyridine poisoning results in bradycardia and/or impaired cardiac conduction [33,34,37,42–47]. Although overdose experience with dihydropyridines other than nifedipine is limited [33,45–48], they would be expected to have effects similar to nifedipine. The exception may be amlodipine where toxic effects may be delayed [46].

Severe poisoning is characterized by hypotension and bradycardia [34,37,40,49,50], hyperglycemia [37,38,40,42,45–47, 49–59] and metabolic acidosis [17,33,42,46,47,49,52,53,56, 59]. Hyperglycemia is due to aforementioned alterations in insulin and carbohydrate homeostasis (see Physiology and Pathophysiology section). In fact, in a recent review of 40 CCA overdoses the degree of hyperglycemia was the best predictor of the composite end points of death, pacemaker requirement, or vasopressor requirement [60]. Dysfunctional carbohydrate metabolism and tissue hypoperfusion result in hyperlacticacidemia. In addition, tissue hypoperfusion can result in cerebrovascular accidents, seizures, renal failure, myocardial infarction, and noncardiogenic pulmonary edema [61].

DIFFERENTIAL DIAGNOSIS

CCA poisoning should be considered in any patient presenting with hypotension and bradycardia. Suspicions that the patient is poisoned with a CCA should be raised even further if there is associated hyperglycemia and acidosis. However, the differential diagnosis of a patient with hypotension and bradycardia includes other toxicologic causes such as beta-blockers, digoxin and other cardiac glycosides, antidysrhythmics, and clonidine. However, nontoxicologic causes such as myocardial disease, hyperkalemia, sepsis, and hypothyroidism should also be considered.

MANAGEMENT

General

Management of a patient with CCA poisoning begins with airway management and maintenance of vital signs. Vascular access should be obtained and continuous blood pressure and cardiac monitoring initiated. Preemptive intubation should strongly be considered in patients with significant ingestions or signs of toxicity due to the potential for rapid deterioration. In bradycardic patients, administration of atropine before intubation may prevent vagal responses from laryngoscopy. An electrocardiogram (ECG) should be obtained. The presence of dysrhythmias or conduction disturbances, which may be as subtle as PR prolongation in some patients, should be noted. Measurements of renal function, electrolytes, complete blood counts, liver function tests, arterial blood gases, and acetaminophen, salicylate, and digoxin levels should be guided by the clinical picture and medical history.

Serum CCA levels are not routinely available and do not help with patient management, but may be necessary for confirmation of the diagnosis. In patients with severe or refractory hypotension, urinary catheterization and central venous catheterization are recommended to guide fluid and vasopressor therapy. Finally, early consultation with a medical toxicologist, regarding medical therapy, and a cardiologist, regarding pacemaker or intra-aortic balloon pump placement, is recommended.

Gastrointestinal Decontamination

Definitive data regarding the utility of gastrointestinal decontamination in overdoses are lacking, and all forms of decontamination carry potential risks. However, CCA overdoses can result in serious morbidity and mortality, so that potential benefits of decontamination may outweigh risks in significant ingestions. Risks and benefits should be considered on a case-by-case basis, and interventions necessary to maintain vital signs take precedence over decontamination. Aspiration is one of the main risks associated with decontamination. Thus, assurance of airway control prior to decontamination is necessary.

Activated charcoal should be administered to all significant ingestions. The greatest benefit of charcoal administration occurs within the first 2 hours after ingestion [62]. However, it may hold benefit, especially for SR preparations, up to 4 hours after ingestion [63]. Gastric lavage should not be used routinely, but considered for recent life-threatening ingestions in patients who have not already vomited [64]. Like laryngoscopy, lavage may theoretically cause bradycardia from vagal effects. Thus, atropine should be given prior to initiation, and lavage should be withheld in patients with existing bradycardia and conduction abnormalities [20].

Large ingestions of SR preparations may provide a gastrointestinal depot of drug causing recurrent cardiovascular compromise, or rise in serum drug levels up to 18 hours after initial decontamination [35,38,49,53,58,65,66]. A rise in serum amlodipine levels has been demonstrated 24.5 hours after ingestion—approximately 22 hours after decontamination [47]. Therefore repeat charcoal doses or whole bowel irrigation (WBI) with polyethylene glycol should be considered for large ingestions of SR products in patients with functioning gastrointestinal tracts [61]. Repeat charcoal dosing has also been recommended in large overdoses of IR products [29]. One or two additional doses of activated charcoal (0.5 g per kg without cathartic) separated by 2 to 4 hours may be sufficient. Because of the large volumes necessary, polyethylene glycol WBI should be administered via nasogastric tube (0.5 L per hour for small children and 1 to 2 L per hour for adults). However, it may be prudent to withhold WBI in patients with hemodynamic compromise [67].

Cardiovascular Support

Hypotension can initially be treated with intravenous crystalloids with close monitoring for fluid overload. Although usually ineffective in severe poisoning [34,38,40,41,58], atropine should be given for symptomatic bradycardia. Treatment beyond general supportive care, intravenous fluids, and atropine will depend on the clinical situation. Seriously poisoned patients may require rapid simultaneous administration of multiple therapies. Transvenous pacing may be attempted, but in significant poisoning there may be failure to capture, and blood pressure may not improve despite an increase in heart rate [34,38].

Vasopressors

The exact sequence of pharmacologic therapies has not been studied. However, healthcare providers generally have the greatest familiarity with dosing and administration of vasopressor agents. Thus, these agents can often be initiated rapidly and may improve cardiovascular instability. Ideally and agent with both α_1- and β-agonist effects should be instituted. Improvements have been noted with dopamine, dobutamine, norepinephrine, isoproterenol, and epinephrine [34,37,49,50, 52,68]. However, no specific agent has demonstrated superiority so it is reasonable for clinicians to start with the agent they

are most familiar with. There is scant information regarding vasopressin utility in CCA poisoning, but based on available data it should not be used as monotherapy in CCA poisoning. Animal models have demonstrated either no improvement in mean arterial pressure [69] or decreased survival [70] with vasopressin compared to saline controls. However, there was improvement in systemic vascular resistance and blood pressure after vasopressin was administered to two patients unresponsive to multiple other therapies [71].

Multiple simultaneous vasoactive agents may be required depending on the hemodynamic response, and require doses much higher than ACLS-based doses [72]. Because vasopressors can result in tachydysrhythmias, increased myocardial oxygen consumption and vasospastic events, these agents should be the first to be weaned from a patient who has stabilized.

Hyperinsulinemic Euglycemia

Hyperinsulinemic euglycemia (HIE) refers to the administration of high-dose regular insulin while maintaining normal serum glucose levels. HIE is thought to overcome the CCA-induced compromise of cardiovascular carbohydrate uptake thus improving hemodynamic embarrassment. The exact mechanisms underlying these actions still remain controversial [73], but may be best described in the following animal studies.

Four animal studies (mongrel dogs) of HIE in verapamil poisoning [10,11,17,74] have been rated as very good to excellent quality by an expert panel [72]. Where survival from poisoning was measured, 100% of animals treated with insulin survived [74]. However, survival with epinephrine [17,74], glucagon [17,74], and calcium [17] was 33%, 0%, and 17%, respectively. Insulin also increased the mean lethal dose of verapamil and time to death compared to epinephrine and glucagon [11]. In these studies HIE improved and sustained cardiac contractility, systolic and diastolic function, and systemic and cardiac blood flow compared to calcium, glucagon, and epinephrine [10,11,17,74]. Insulin improved myocardial metabolism and function without increasing myocardial oxygen consumption [10,11]. Epinephrine, glucagon, and calcium however contribute to oxygen wasting [17].

The first report of HIE therapy, published in 1999, included five CCA-poisoned patients who failed to respond to other therapies [48]. The benefit of HIE was striking. Insulin dosing included a 10 to 20 IU bolus with a 25-g bolus of glucose followed by an infusion of 0.1 to 1.0 IU per kg per hour (mean 0.5 IU per kg per hour) and dextrose 10 to 75 g per hour (mean 28.4 g per hour). One patient failed to improve with respiratory support, crystalloids, atropine, calcium, and glucagon. After initiation of HIE blood pressure improved, complete heart block resolved, and echocardiographically measured ejection fraction increased from 10% to 30%. Many other cases have been published and the clinical data supporting HIE have recently been reviewed [73,75]. The data provides multiple examples of CCA-poisoned patients improving with HIE therapy after failing treatments such as atropine, pacing, vasopressors, calcium, glucagon, and phosphodiesterase inhibitors.

Clinical improvement is gradual and may take 30 minutes or more. However, one patient who failed to respond to dopamine, norepinephrine, calcium, and glucagon showed a dramatic response within 15 minutes of receiving a 10-fold dosing error of insulin (1,000 IU) [76]. Patients responding to insulin therapy demonstrate improved blood pressure, myocardial contractility, and metabolic acidosis, whereas effects on bradycardia and cardiac conduction are variable [73].

Failures of HIE therapy have also been reported [77]. Our lack of knowledge regarding optimum dosing of insulin has been suggested as a reason for failures with HIE [78]. Canine studies of verapamil toxicity employed insulin doses of up to 16 IU per kg per hour, but a dose–response relationship for insulin has not been determined [78]. The timing of HIE administration may also be a consideration. In several failures HIE was initiated multiple hours after ingestion when significant hemodynamic compromise was already present. This suggests a threshold point in CCA poisoning where there may be no beneficial intervention once that threshold is crossed. Therefore, HIE should be instituted well before profound shock supervenes. Although an optimal dosing scheme has yet to be established, a rational starting point is an initial insulin bolus of 1 IU per kg with 25 g of dextrose, followed by an infusion at 1 U per kg per hour and 0.5 g per kg per hour of dextrose [61,73]. It is believed supraphysiologic insulin doses are required to overcome CCA inhibition of insulin responsive GLUTs (see Physiology and Pathophysiology section) [19]. Increasing the insulin dose may be of benefit if response is insufficient. Serum glucose should be monitored closely and dextrose infusions adjusted to maintain normal ranges.

Hypoglycemia and hypokalemia, expected adverse effects of HIE, can be easily detected and treated. The safety of HIE therapy was recently demonstrated in a prospective observational study [79]. Serum glucose and potassium were monitored every 30 minutes until stable and then 1 to 2 hourly thereafter. Out of seven patients only one episode of hypoglycemia (43.5 mg per dL) occurred (occurring 33.5 hours after ingestion when the maximal effects of CCA-induced insulin resistance would be waning). Hypokalemia (2.5 to 3.5 mmol per L) occurred in two patients without any clinical significance. However, it has been suggested that mild hypokalemia may provide a beneficial effect in CCA poisoning [48,59].

Hypoglycemic effects of insulin last for hours after infusions are discontinued which requires continued monitoring of blood glucose during this period. Aggressive correction of insulin-induced hypokalemia is unnecessary unless the patient is symptomatic, or potassium level falls below an arbitrarily suggested level of 2.5 mEq per L [48].

Calcium

The goal of calcium therapy is to increase extracellular calcium concentrations thus increasing calcium influx through any unblocked calcium channels. Calcium has demonstrated effectiveness in animal models [80–83], and improvement reported in human cases [37,38,41,44,56,84,85]. However, responses are variable and often short-lived, and patients with significant toxicity often fail to improve with calcium alone [28,34,40,43,49]. Conduction disturbances, contractility, and blood pressure, may be improved, but generally, there is no increase in heart rate [34,40,49,58]. Optimum dosing has yet to be established, and 4.5 to 95.3 mEq were used in one case series without an identifiable dose–response [34].

Calcium chloride compared to calcium gluconate contains three times the amount of elemental calcium on a milliequivalent basis (10% calcium chloride: 272 mg elemental calcium or 13.6 mEq per 1 g ampule; 10% calcium gluconate: 90 mg elemental calcium or 4.5 mEq per 1 g ampule). However, it is recommended to only give calcium chloride via a central venous catheter [84]. Calcium gluconate can be given via a peripheral line.

Optimum calcium dosing is not well established. Initial doses are generally given as boluses (10 to 20 mL of 10% calcium chloride, or 30 to 60 mL of 10% calcium gluconate) [46,86–88]. Additional boluses may be given every 10 to 20 minutes. Some authors suggest more aggressive dosing of 1 g every 2 to 3 minutes until clinical response is seen [37]. Boluses should be given over a 5-minute period in conjunction with cardiac monitoring as rapid infusions have resulted in hypotension, atrioventricular dissociation, and ventricular fibrillation [89,90]. The effects of boluses may be transient, and

a constant infusion required [37,46,86,87]. Infusions can be started at 0.4 mL per kg per hour for calcium chloride and 1.2 mL per kg per hour for calcium gluconate and titrated to effect. Additional boluses can be given as needed. Calcium levels should be monitored. One author recommends maintaining serum ionized calcium levels approximately twice normal [91]. Raising serum ionized calcium to 2 to 3 mEq per L improves canine cardiac performance in verapamil poisoning [17,80] and is a reasonable goal to attain. It may be necessary to continue therapy despite high serum calcium levels if the patient is only responding to calcium administration. Significantly poisoned patients have tolerated high serum calcium levels without untoward effect [35,37,44,66], including one patient who obtained a peak serum calcium level of 23.8 mg per dL [38]. However, a patient in another report achieved a peak calcium level of 32.3 mg per dL and developed anuric renal failure and eventually died [92]. It has been recommended to stop calcium infusions if no beneficial effect is observed [93]. In addition, calcium should not be administered to a patient with proven or potential digoxin toxicity.

Glucagon

Glucagon possesses both inotropic and chronotropic effects [94], and experimentally increases heart rate, cardiac output, and reverses AV nodal blocks in CCA poisoning [95]. Several case reports noted improvement with glucagon therapy [50,51,65,96], but failures are also reported [52,58,59,97]. Five to ten milligrams (150 µg per kg) given intravenously over 1 to 2 minutes is a typical starting dose [95]. Cardiovascular effects of glucagon last only 10 to 15 minutes [98,99], so repeat boluses may be required every 5 to 10 minutes followed by a continuous infusion of 2 to 10 mg per hour (50–100 µg per kg per hour) [20,95]. Glucagon is a potent emetic [98], so airway control should be ensured before administration. Hyperglycemia and hypokalemia may also be observed with glucagon administration [98].

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors (PDI) such as inamrinone (amrinone) and milrinone increase cytosolic calcium and improve inotropy. Phosphodiesterase inhibitors have been used in combination with other therapies to treat CCA-poisoned patients [54,55], and appear to be effective in animal models [100,101]. However, they can be difficult to titrate and cause vasodilation and hypotension.

RESCUE AND EXPERIMENTAL THERAPIES

Nonpharmacologic Therapies

If available, intra-aortic balloon counterpulsation [57], or cardiopulmonary bypass [58,102] may provide a bridge to survival in patients unresponsive to other therapies.

Pharmacologic Therapies

4-Aminopyridine

4-Aminopyridine is an orphan drug used to treat spinal cord injury and multiple sclerosis. It improves contractility by indirectly increasing intracellular calcium levels and has shown benefit in animal studies of verapamil toxicity [103,104] and in one human case report [24]. Unfortunately, it causes seizures and has a narrow therapeutic index. It may be considered if all other treatments are failing.

Intravenous Lipid Emulsion

Perhaps, the most promising new therapy for CCA poisoning is intravenous lipid emulsion (ILE). Intravenous lipids have traditionally been used as a source of free fatty acids in parenteral nutrition. A chance observation led to the finding that ILE is beneficial in the treatment of local anesthetic-induced cardiac arrest [105]. Multiple animal studies followed demonstrating dramatic results with ILE for local anesthetic toxicity. This led to the incorporation of ILE into anesthesiology guidelines for the treatment of local anesthetic cardiotoxicity [106].

Intravenous lipids have recently been investigated in verapamil toxicity. In a rat model, ILE significantly prolonged survival and doubled the median lethal dose of verapamil [107]. Intravenous lipid emulsion dramatically improved blood pressure and survival rate compared with saline in dogs pretreated with atropine and calcium chloride [108]. The two case reports of ILE for CCA poisoning have suggested a benefit [109,110].

Proposed mechanisms of ILE therapy include creation of a "lipid sink" where lipid soluble toxins are sequestered, augmenting cardiac energy supplies, and increasing intracellular calcium in cardiac myocytes [111]. In addition, ILE is inexpensive and readily available. The main safety concern regarding ILE therapy is pulmonary fat emboli. The one study to specifically examine this failed to demonstrate signs of fat emboli with ILE therapy [112].

Although experimental evidence for ILE for CCA poisoning is currently limited, it should be considered for patients who are failing other more traditional therapies. Dosing recommendations can be found at www.lipidrescue.org.

DISPOSITION

Patients with signs or symptoms of toxicity require ICU admission. Disposition of symptomatic patients depends on the formulation ingested. Patients with large or intentional ingestions of SR products or amlodipine should undergo appropriate decontamination and 24 hours of observation in a closely monitored setting. Patients with small unintentional ingestions of SR products may be medically cleared after appropriate decontamination if they remain asymptomatic with normal vital signs and ECGs for 8 to 12 hours. Close attention should be paid to subtle ECG signs of toxicity such as PR prolongation. Patients ingesting non-SR products may be cleared after 6 to 8 hours of observation if normal vital signs and ECGs are maintained.

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CHAPTER 127 ■ CARDIAC GLYCOSIDE POISONING

MARK A. KIRK AND BRYAN S. JUDGE

Cardiac glycosides (CGs) are naturally occurring substances whose medicinal benefits have been recognized for centuries [1]. Digoxin is the major CG used for medicinal purposes today. It is most widely used in the treatment of congestive heart failure and acute atrial fibrillation associated with a rapid ventricular response rate [2]. Although digoxin is responsible for most cases of CG poisoning, exposure to plant (i.e., dogbane, foxglove, lily of the valley, oleander, red squill, and Siberian ginseng) and animal (i.e., *Bufo* toad species) sources and topical aphrodisiacs can also result in serious toxicity [3–5].

PHARMACOLOGY

Digoxin exerts a positive inotropic effect, thereby enhancing the force of myocardial contraction. Direct effects of digoxin

include prolongation of the effective refractory period in the atria and the atrioventricular (AV) node, which diminishes the conduction velocity through those regions. CGs are readily absorbed through the gastrointestinal tract; digoxin has up to 80% bioavailability [6]. Digoxin has a volume of distribution (V_d) of 5.1 to 7.4 L per kg [7] and a half-life of 36 to 48 hours [2]. The generally accepted therapeutic serum concentration range for digoxin is 0.8 to 2.0 ng per mL for inotropic support in patients with left ventricular dysfunction. Higher concentrations (1.5 to 2.0 ng per mL) may be needed for ventricular rate control in patients with atrial dysrhythmias. Digoxin is primarily eliminated by the kidneys. In patients with renal dysfunction, digoxin clearance is reduced. Serum digoxin concentrations can be altered by numerous drug interactions [8–10].

Toxicity results from an exaggeration of therapeutic effects [6]. Cardiac glycosides bind to and inactivate the sodium–potassium adenosine triphosphatase pump (Na^+–K^+-ATPase) on cardiac cell membranes. This pump maintains the electrochemical membrane potential, vital to conduction tissues, by concentrating Na^+ extracellularly and K^+ intracellularly. When Na^+–K^+-ATPase is inhibited, the Na^+–calcium exchanger removes accumulated intracellular sodium in exchange for calcium. This exchange increases sarcoplasmic calcium and is the mechanism responsible for the positive inotropic effect of digitalis. Intracellular calcium overload causes delayed after depolarizations and gives rise to triggered dysrhythmias. Increased vagal tone and direct AV depression may produce conduction disturbances. The decreased refractory period of the myocardium increases automaticity.

CLINICAL PRESENTATION

Differences between the presentations of patients with CG poisoning due to a single acute ingestion and those with chronic toxicity resulting from excessive therapeutic doses are illustrated in Table 127.1. Diagnosing chronic CG toxicity is more difficult because the presentation may mimic more common illnesses, such as influenza or gastroenteritis. Patients with chronic CG toxicity may present with constitutional, gastrointestinal, psychiatric, or visual complaints that may not be recognized as signs of digitalis toxicity. Symptoms most commonly reported include fatigue, weakness, nausea, anorexia, and dizziness [11]. Neuropsychiatric signs and symptoms include headache, weakness, vertigo, syncope, seizures, memory loss, confusion, disorientation, delirium, depression, and hallucinations [12]. The most frequently reported visual disturbances are cloudy or blurred vision, loss of vision, and yellow-green halos or everything appearing "washed in yellow" (xanthopsia) [13].

Cardiac manifestations of CG toxicity are common and potentially life threatening. An extremely wide variety of dysrhythmias has been reported [14,15]. Dysrhythmias frequently associated with CG toxicity include premature ventricular contractions, paroxysmal atrial tachycardia or atrial fibrillation with a conduction block, junctional tachycardia, sinus bradycardia, AV nodal blocks, ventricular tachycardia, and ventricular fibrillation. Atrial tachycardia (enhanced automaticity) with variable AV block (impaired conduction), atrial fibrillation with an accelerated or slow junctional rhythm (regularization of atrial fibrillation), and fascicular tachycardia are highly suggestive of CG toxicity [16,17]. Bidirectional ventricular tachycardia, a narrow-complex tachycardia with right bundle-branch morphology, is highly specific, but not pathognomonic for digitalis toxicity [14].

True end-organ digoxin sensitivity is seen with myocardial disease, myocardial ischemia, and metabolic or electrolyte disturbances [18]. Hypokalemia, hypomagnesemia, and hypercalcemia predispose to toxicity [2]. The elderly are at increased risk, whereas renal impairment, hepatic disease, hypothyroidism, chronic obstructive pulmonary disease, and drug interactions alter sensitivity to CGs [1].

DIAGNOSTIC EVALUATION

Essential laboratory tests include serum digoxin concentrations, electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, and electrocardiogram. Additional laboratory tests should be obtained as clinically indicated. Serum digoxin concentrations can assist in the diagnosis of CG poisoning but often are unreliable indicators of toxicity [17]. A therapeutic concentration does not exclude poisoning, as predisposing factors can cause an individual to become poisoned despite a concentration within the therapeutic range. Conversely, high serum

TABLE 127.1

CHARACTERISTICS OF ACUTE AND CHRONIC CARDIAC GLYCOSIDE TOXICITY

Clinical finding	Acute toxicity	Chronic toxicity
Gastrointestinal toxicity	Nausea, vomiting	Nausea, vomiting
Central nervous system toxicity	Headache, weakness, dizziness, confusion, and coma	Confusion, coma
Cardiac toxicity	Bradydysrhythmias, supraventricular dysrhythmias with AV block; ventricular dysrhythmias are uncommon	Virtually any dysrhythmia (ventricular or supraventricular dysrhythmias with or without AV block); ventricular dysrhythmias are common
Serum potassium	Elevated but may be normal (high concentrations correlated with toxicity)	Low or normal (hypokalemia secondary to concomitant diuretic use)
Serum digoxin concentration	Markedly elevated	May be within "therapeutic" range or minimally elevated

AV, atrioventricular.
Adapted and combined from references [1,11,12,14,32].

digoxin concentrations after an acute ingestion are not always indicative of toxicity [19]. Digoxin follows a two-compartment model of distribution, with relatively rapid absorption into the plasma compartment and then slow redistribution into the tissue compartment [2]. Serum digoxin concentrations most reliably correlate with toxicity when obtained after distribution is complete, which occurs 6 hours or more after oral or intravenous digoxin administration.

Naturally occurring digitalis glycosides from plants and animals can cross-react with the digoxin assay. The degree of cross-reactivity is unknown, and no good correlation has been established between serum concentrations of these glycosides and toxicity [5]. A false-positive digoxin assay (usually less than 3 ng per mL), may occur in neonates and patients with renal insufficiency, liver disease, and pregnancy [20–22] because of endogenous digoxin-like immunoreactive factors.

Hyperkalemia may be a better indicator of end-organ toxicity than the serum digoxin concentration in the acutely poisoned patient [23]. In contrast, hypokalemia and hypomagnesemia are commonly seen in the chronically intoxicated patient, presumably as a result of concomitant diuretic use.

MANAGEMENT

The management of CG poisoning includes supportive care, prevention of further drug absorption, antidotal therapy, and safe disposition. Meticulous attention to supportive care and a search for easily correctable conditions, such as hypoxia, hypoventilation, hypovolemia, hypoglycemia, and electrolyte disturbances, are top priorities. All patients should have vascular access established and continuous cardiac monitoring. Patients with clinical toxicity or elevated serum digoxin concentrations should be admitted to the intensive care unit.

Prevention of further drug absorption should be addressed after life support measures have been initiated. Gastric lavage has little if any benefit in the management of digoxin toxicity. Activated charcoal effectively binds cardiac glycosides, and multiple doses of activated charcoal enhance intestinal digoxin elimination after oral and intravenous digoxin administration [24,25]. A recent study demonstrated that activated charcoal favorably impacts the pharmacokinetic profile of CGs in patients self-poisoned with seeds from the yellow oleander tree [26]. However, further research is necessary to clarify whether patients poisoned with yellow oleander will benefit from activated charcoal since clinical outcomes reported in previous studies have been conflicting [27,28].

Conventional treatment of bradydysrhythmia includes the use of atropine, isoproterenol, and cardiac pacing. However, atropine sulfate has been used with variable success in patients with digitalis toxicity exhibiting AV block [29], isoproterenol may increase ventricular ectopy and cardiac tissue may be unresponsive to electrical pacing, the fibrillation threshold may be lowered, and the pacing wire itself may induce ventricular fibrillation [30]. Digoxin-specific antibody fragments (Fab) are now considered first-line therapy in patients with symptomatic bradycardia [31].

Digoxin-specific antibody Fab is also the treatment of choice for life-threatening ventricular dysrhythmias. If this therapy is not immediately available, phenytoin and lidocaine, which depress increased ventricular automaticity without slowing AV nodal conduction, should be the initial therapy [17,32]. Amiodarone was successful in two cases refractory to other antidysrhythmics [33,34]. Intravenous magnesium, 2 to 4 g (10 to 20 mL of a 20% solution) over 1 minute, may also be useful [35]. Quinidine and procainamide are contraindicated in digitalis toxicity because they depress AV nodal conduction and may worsen cardiac toxicity [1]. Electrical cardioversion of the digitalis-toxic patient should be performed with extreme caution and considered a last resort. A low-energy setting (e.g., 10 to 25 W per second) should be used and preparations made to treat potential ventricular fibrillation [32].

Hyperkalemia is common in patients with acute digoxin poisoning, and empiric administration of supplemental potassium should be avoided [36]. This increase in serum potassium concentration reflects a change in potassium distribution and not an increase in total body potassium stores. Significant hyperkalemia due to acute overdose is another indication for digoxin-specific antibody Fab. If digoxin-specific antibody Fab are not immediately available and the patient has hyperkalemia with associated electrocardiogram changes, intravenous glucose and insulin, sodium bicarbonate, continuous inhaled β agonists such as albuterol (if there is no tachydysrhythmia or ectopy), and sodium polystyrene sulfonate should be administered. The use of intravenous calcium to treat hyperkalemia in CG toxic patients remains controversial and has been previously avoided by many clinicians because additional calcium has been reported to enhance cardiac toxicity [18]. However, some authors have questioned this dogma—citing animal studies and human case reports that document no untoward effects when calcium is administered in the setting of CG toxicity—and recommend the use of intravenous calcium in those patients with CG toxicity who have life-threatening hyperkalemia with significant changes on the electrocardiogram such as loss of P waves or widening of the QRS [37]. Hemodialysis may be of benefit in a CG-poisoned patient with renal failure and hyperkalemia.

Supplemental potassium may be beneficial in chronic digitalis toxicity when diuretic-induced hypokalemia is a factor. Potassium should be administered cautiously, as renal dysfunction may be the cause of digitalis toxicity. Hypomagnesemia is common in patients with chronic CG toxicity, and supplemental magnesium is recommended for such patients [38].

Digoxin-specific antibody Fab therapy is indicated for patients with dysrhythmias that threaten or result in hemodynamic compromise and patients with serum potassium greater than 5.0 to 5.5 mEq per L after acute CG overdose [39,40]. Chronically poisoned patients who are asymptomatic can often be managed with discontinuation of digoxin and close observation. The threshold for treatment with digoxin-specific antibody Fab should be lower in those patients with signs of cardiac toxicity or who have predisposing conditions such as chronic pulmonary disease, hypokalemia, hypothyroidism, renal dysfunction, or underlying cardiac disease [11]. Animal studies and case reports suggest digoxin-specific antibody Fab may be an effective treatment for patients poisoned by plant or animal sources of CG [3,5].

Digoxin-specific antibody Fab can reverse digitalis-induced dysrhythmias, conduction disturbances, myocardial depression, and hyperkalemia. In a multicenter study, 90% of patients with digoxin or digitoxin toxicity had a complete or partial response to digoxin-specific antibody Fab therapy [39]. Complete resolution of toxicity occurred in 80% of the patients, and partial response occurred in 10%. The time to initial response from end of digoxin-specific antibody Fab infusion was within 1 hour (mean 19 minutes), and the time to complete response was 0.5 to 6.0 hours (mean: 1.5 hours). Treatment failures have been attributed to inadequate or delayed dosing, moribund clinical state before digoxin-specific antibody Fab therapy, pacemaker-induced dysrhythmias, and incorrect diagnosis of digitalis toxicity [39,41].

Digoxin-specific antibody Fab dosage (number of vials) calculations are based on the serum digoxin concentration or

estimated body load of digoxin. It is assumed that equimolar doses of antibody fragments are required to achieve neutralization [42]. A 40-mg dose of digoxin-specific antibody Fab (one vial) binds 0.6 mg of digoxin. The number of vials required can be calculated by dividing the total body burden by 0.6. The body burden can be estimated from the milligram amount of an acute ingestion or by multiplying the serum digoxin concentration (ng per mL) by the volume of distribution of digoxin (= 5.6 L per kg times the body weight in kg) and dividing by 1,000.

In the largest study of Fab for digoxin poisoning (n = 150, mean serum concentration of 8 ng per mL), the dose of Fab required to reverse digoxin toxicity was five vials with a range from 3 to 20 vials [39]. A severely toxic patient in whom the quantity ingested acutely is unknown should be given 5 to 10 vials at a time and the clinical response observed. If cardiac arrest is imminent or has occurred, the dose can be given as a bolus. Otherwise, it should be infused over 30 minutes. In contrast, patients with chronic therapeutic overdose often have only mildly elevated digoxin concentrations and respond to one to two vials of digoxin-specific antibody Fab. The recommended dose for a given patient can be determined using the tables in the package insert or by contacting a regional poison center or toxicology consultant.

The dose of digoxin-specific antibody Fab needed to treat nondigoxin CG poisoning is unknown but likely to be greater than that necessary for digoxin poisoning. Starting with 5 to 10 vials and repeating this dose as necessary is a reasonable approach.

Free digoxin concentrations are decreased to zero within 1 minute of digoxin-specific antibody Fab therapy, but total serum digoxin concentrations are markedly increased [39,43]. Because most assay methods measure total (bound and free) digoxin, very high digoxin concentrations are seen after digoxin-specific antibody Fab treatment, but they have no correlation with toxicity [43]. Serum concentrations may be unreliable for several days after digoxin-specific antibody Fab therapy [44].

The digoxin–Fab complex is excreted in the urine and has a half-life of 16 to 20 hours [45]. In patients with renal failure, elimination of the digoxin–Fab complex is prolonged and free digoxin concentrations gradually increase over 2 to 4 days after digoxin-specific antibody Fab administration [46]. In one report of 28 patients with renal impairment given digoxin-specific antibody Fab, only one patient had recurrent toxicity, which occurred 10 days after digoxin-specific antibody Fab treatment and persisted for 10 days [47]. Monitoring of free digoxin concentrations may be beneficial for titrating effect in those patients reliant on the inotropic action of digoxin, detecting rebound toxicity in patients with renal impairment, assessing the need for further treatment with digoxin-specific antibody Fab, or in guiding the reinstitution of digoxin therapy [48]. Hemodialysis has not been reported to enhance digoxin–Fab complex elimination.

Digoxin-specific antibody Fab therapy has been associated with mild adverse drug events such as rash, flushing, and facial swelling [39,41]. However, neither acute anaphylaxis nor serum sickness has been described [41]. Before digoxin-specific antibody Fab administration, an asthma and allergy history should be obtained. Intradermal skin testing should be considered in high-risk patients. If a patient with a positive skin test is dying, however, the risk–benefit ratio obviously favors treatment [41]. A precipitous drop in the serum potassium, recurrence of supraventricular tachydysrhythmias previously controlled by digoxin, and development of cardiogenic shock in a patient dependent on digoxin for inotropic support have all been associated with digoxin-specific antibody Fab therapy [39]. Recurrent toxicity has been observed in 3% of patients [41]. In most, it was attributed to inadequate initial dose of digoxin-specific antibody Fab dosing and reversed with a repeat dose.

Patients who receive digoxin-specific antibody Fab require continued monitoring in an intensive care unit for at least 24 hours. Those with elevated drug concentrations resulting from chronic therapy who are hemodynamically stable can be observed on a telemetry unit. Discontinuing the use of digoxin or decreasing the dose, modifying predisposing factors, and closely monitoring subsequent therapy are necessary to avert further toxic episodes. Patients with suicidal ingestions should have a psychiatric evaluation before discharge.

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CHAPTER 128 ■ CHOLINERGIC POISONING

CYNTHIA K. AARON

Cholinergic (acetylcholinesterase inhibitor) agents are used in medicine, as insecticides, and as "nerve agent" chemical weapons. Most poisonings are accidental dermal contamination during agricultural use of pesticides [1]. The majority of suicide attempts are ingestions [2]. Food-borne exposures have produced epidemics such as "Ginger Jake paralysis" (delayed neuropathy) due to contamination of an alcoholic drink with triorthocresyl phosphate [3] and a large epidemic of mild-to-moderate symptoms related to use of the insecticide aldicarb on watermelons [4].

PHARMACOLOGY

Cholinesterase inhibitors act by blocking the active site of acetylcholinesterase (AChE). Organophosphates form a covalent phosphate linkage at the enzyme active site. Enzyme regeneration occurs by either de novo synthesis, hydrolysis of the serine–organophosphorus bond, or oxime regeneration. However, over 24 to 48 hours, most phosphorylated molecules *age* or become resistant to reactivation by oxime therapy. Carbamates are reversible inhibitors of AChE, occupying (but not modifying) the catalytic region of the enzyme. AChE activity is restored when the carbamate spontaneously leaves the enzyme's active site [5]. AChE inhibitors such as tacrine, rivastigmine, donepezil, and galantamine have been used for treatment of Alzheimer's dementia. The characteristics and treatment of exposure to these products is covered at the end of this chapter.

Inhibition of AChE allows the neurotransmitter acetylcholine to accumulate and remain active in the synapse, resulting in sustained depolarization of the postsynaptic neuron or effector organ. This effect occurs in the central nervous system (CNS) as well as at muscarinic sites in the peripheral nervous system, nicotinic sites in the sympathetic and parasympathetic ganglia, and nicotinic sites at the neuromuscular junction. In general, effects at muscarinic sites are sustained, whereas nicotinic sites are stimulated and then depressed (hyperpolarization block). Signs and symptoms of cholinergic toxicity typically appear when 60% to 80% of cholinesterase activity has been inhibited [6]. The pharmacologic and toxicologic effects of acetylcholinesterase inhibitor are an extension of their mechanism of action (Table 128.1).

In addition to acute cholinergic effects, organophosphates cause two other toxic effects. Intermediate syndrome (IMS) is a recurrence of weakness that occurs hours to days after a serious organophosphate exposure [7]. Some authors have suggested that IMS is caused by inadequate oxime therapy when serum organophosphate concentrations remain elevated due to redistribution, altered metabolism, or decreased clearance [8]. It is also possible that IMS is due to desensitization block with downregulation and eventual decrease in the nicotinic receptor activity. Since the nicotinic receptor has five subunits, there is probably significant polymorphism at this receptor affecting clinical response [9].

TABLE 128.1

PHARMACOLOGIC EFFECTS OF CHOLINESTERASE INHIBITION RECEPTOR TYPE

Location	Effects
Muscarinic (increased stimulation)	
Pupils	Miosis (constriction)
Ciliary body	Blurred vision
Exocrine glands	Increased secretions
Lacrimal	Tearing
Salivary	Salivation
Respiratory	Bronchorrhea, rhinorrhea
Heart	Bradycardia
Smooth muscle	Contraction
Bronchial	Bronchoconstriction
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea
Bladder	Incontinence, frequency
Sphincter of Oddi	Pancreatitis
Central nervous system	Variable[a]
Nicotinic (stimulation; then depression)	
Skeletal muscle	Weakness, cramps, fasciculation, paralysis
Sympathetic ganglia	Tachycardia, hypertension; then hypotension
Central nervous system	Variable symptoms from anxiety and restlessness to confusion, obtundation, coma, and seizures[a]

[a]Relative contributions of nicotinic and muscarinic receptors to central nervous system effects are unclear.

The second noncholinergic effect is organophosphorus-induced delayed peripheral neuropathy (OPIDN). This is a delayed peripheral neuropathy, which appears to be mediated by a membrane-bound specific "neuropathy target esterase." Organophosphates that have been associated with OPIDN are aryl organophosphorus esters that contain either a pentavalent phosphorus atom (type I, including derivatives of phosphoric, phosphonic, and phosphoramidic acids, or phosphorofluoridates) or a trivalent phosphorus atom (type II or phosphorus acid derivatives). This neuropathy primarily involves motor fibers. Histologic analysis shows progressive neuronal degeneration, beginning with axonal swelling followed by demyelination, axonal degeneration, and neuronal cell body death and Wallerian degeneration or "dying back" phenomenon [10].

CLINICAL MANIFESTATIONS

Excessive acetylcholine produces symptoms of muscarinic and nicotinic excess. These clinical effects are outlined in Table 128.2. One mnemonic used to describe the muscarinic toxidrome is DUMBELS (*d*iarrhea, *u*rination, *m*iosis, *b*ronchospasm, *e*mesis, *l*acrimation, *s*alivation). Miosis may be the most sensitive marker for moderate or severe exposure to a acetylcholinesterase inhibitor [11]. Lacrimation, rhinorrhea, salivation, and profuse sweating are common in moderate to severe poisoning. Abdominal cramping, diarrhea, and vomiting are very common with severe poisoning. Fasciculations are typically observed in severe overdoses.

Respiratory failure is a common cause of death from acetylcholinesterase inhibitor poisoning [2]. Cholinergic excess has direct deleterious effects on the respiratory center; causes bronchial muscle spasm and noncardiogenic pulmonary edema with exuberant mucus production; and severe respiratory muscle impairment. Respiratory failure may be further complicated by aspiration.

Cardiac toxicity has been increasingly described as a complication of organophosphate poisoning. There are three phases of reported toxicity including a brief period of intense sympathomimetic tone, a period of enhanced parasympathetic activity, and corrected QT (QTc) interval prolongation with potential for torsade de pointes. Prolongation of the QTc is a marker of severity and patients with a QTc greater than 440 milliseconds require higher doses of atropine and have a higher mortality than those a QTc less than 440 milliseconds [12]. Electrocardiographic abnormalities including nonspecific ST-T changes, tachydysrhythmias, bradydysrhythmias, and polymorphic (torsade de pointes) ventricular tachycardia have been reported [13]. The effect on blood pressure is variable. Patients poisoned with dimethoate have an initial benign course but develop refractory hypotension and cardiogenic shock within 36 to 48 hours [2].

The CNS effects of cholinergic poisoning include altered mental status seizures and coma [2]. Dystonias and choreoathetoid movements have also been observed [14]. Less severe

TABLE 128.2

SYMPTOMS OF CHOLINERGIC POISONING

Exposure only	Mild poisoning	Moderate poisoning	Severe poisoning
No symptoms	Can walk Fatigue Headache Dizzy Nausea Vomiting Numbness Sweating Salivation Chest tightness Abdominal cramps Diarrhea ChE 20%–50% of normal	Cannot walk Weakness Difficulty speaking Fasciculations Miosis ChE 10%–20% of normal	Unconscious Unreactive pupils Fasciculations Flaccid paralysis Secretions mouth/nose Moist rales Respiratory distress Seizures ChE < 10% of normal

ChE, RBC cholinesterase.

acute manifestations include anxiety, agitation, emotional lability, headaches, insomnia, tremor, difficulty in concentrating, slurred speech, ataxia, and hyperreflexia or hyporeflexia. In some cases, acute organophosphate poisoning may produce longer-lasting neuropsychiatric sequelae [15]. This has been labeled the chronic organophosphorus-induced neuropsychiatric disorder (COPIND). These problems seem most severe after serious acute intoxications and usually resolve within 1 year [15].

Cholinergic signs and symptoms typically begin minutes to hours after exposure [2]. Symptom onset is rarely more than 12 hours after exposure. Onset may be delayed for lipophilic compounds (e.g., fenthion, dichlofenthion, leptophos) [2] or compounds that require hepatic metabolism to a more toxic intermediate (e.g., parathion is metabolized to paraoxon) [16]. Progressive or prolonged symptoms raise the suspicion of continued absorption of the poison.

Life-threatening cholinergic symptoms from organophosphate toxicity generally abate within 1 to 3 days, although many cases requiring weeks of intensive care are reported [17]. Symptoms usually resolve within 12 to 48 hours after exposure to carbamates and other reversible cholinesterase inhibitors [18].

The intermediate syndrome, characterized by weakness of neck muscles, motor cranial nerves, proximal limb muscles, and respiratory muscles, but without prominent muscarinic findings beginning 24 to 96 hours after the onset of poisoning and lasting 4 to 18 days has been described [8]. An early clinical indication of this syndrome is that affected patients are unable to lift their heads up from their beds [17].

Delayed neuropathy occurs 1 to 3 weeks after the acute cholinergic crises. Patients may initially recover then show progressive signs and symptoms of OPIDN. Since this is a dying back axonopathy that usually spares the neuronal cell body, the peripheral neuropathy is characterized by both paresthesias and motor dysfunction occurring first in the longest skeletal nerves with development of foot drop and a high-stepping gait. Symptoms develop slowly and can be divided into three phases: progressive, stationary, and improvement. During the progressive phase, patients have a peripheral sensory neuropathy with complaints of burning, tightness, or pain in the legs and feet. This is followed by numbness and tingling. Subsequently, motor weakness develops, with weakness and atrophy of the peroneal muscles causing a foot drop. After approximately 1 week, the paresis may ascend symmetrically into the upper extremities. The sensory loss may occur in a stocking–glove distribution, and the patient loses proprioception. With time, a positive Romberg's sign and loss of lower-extremity deep tendon reflexes may develop. Flaccid paralysis may occur in severe cases. During the stationary phase, paresis may persist or resolve within 2 to 9 weeks, and motor findings may cease to progress. This may occur over 3 to 12 months. The improvement phase may begin 6 to 18 months after exposure. Partial or complete motor function returns in reverse order of loss. During this phase, central cord or brain lesions may be unmasked and spasticity may develop [19].

DIAGNOSTIC EVALUATION

The diagnosis of the cholinergic poisoning is based on a history of exposure, clinical findings (toxidrome), and improvement after appropriate antidotal therapy. The primary laboratory studies for evaluating anticholinesterase poisoning are plasma cholinesterase (also known as butyrylcholinesterase or pseudocholinesterase) and red blood cell (RBC) acetylcholinesterase. These tests are not rapidly available in most clinical settings. Both may be used to confirm the clinical diagnosis. RBC acetylcholinesterase has a similar structure to synaptic acetylcholinesterase and it has been validated as a surrogate for synaptic acetylcholinesterase [20].

Plasma cholinesterase is synthesized in the liver. It falls and recovers more rapidly than RBC cholinesterase. Only transient decreases of RBC and plasma cholinesterase occur with carbamate poisoning, because inactivated AChE spontaneously reactivates with plasma elimination half-lives of 1 to 2 hours [21].

In suspected cholinesterase inhibitor poisoning, plasma and RBC acetylcholinesterase levels should be sent for laboratory determination initially and repeated if the clinical course is atypical [22]. Blood for cholinesterase determination should be drawn into a fluoride free tube as fluoride inactivates enzyme systems. Samples should be spun down and frozen for storage. The assaying laboratory should be contacted to obtain specific drawing and storing instructions.

Acute exposures are usually classified based on the degree of depression of RBC cholinesterase: mild (20% to 50% of baseline), moderate (10% to 20% of baseline), and severe (less than 10% of baseline) (see Table 128.2). An EMG using repetitive tetanic nerve stimulation can be done to characterize the block and to estimate the amount of enzyme inhibition [23]. Since there is a wide range for normal RBC cholinesterase level (substantial interindividual variation), a person's baseline needs to be established if return to working with pesticides is a consideration. [24] Workers should be removed from exposure until RBC cholinesterase is at least 75% of their baseline values [25]. Workers who do not have an established RBC cholinesterase baseline should not return to work until their RBC cholinesterase levels have reached a plateau.

Several organophosphates are metabolized to *p*-nitrophenol that can be easily detected in the urine soon after poisoning [26]. Organophosphate concentrations can be measured in serum [27], but contribute little to patient management. These measurements can be useful in determining residual organophosphate residue in a patient with prolonged signs of toxicity and perhaps whether oxime therapy needs to be continued, particularly when combined with the ability to reactivate the AChE [23]. Supplemental studies include serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, lipase, arterial blood gases, electrocardiography, and chest radiography.

The intermediate syndrome is diagnosed by clinical findings associated with a reproducible EMG-nerve conduction study using repeated submaximal tetanic nerve stimulation and measuring compound muscle action potentials [28]. No specific laboratory studies are available for evaluating OPIDN. Electromyography (EMG) may help to determine the extent of the peripheral neuropathy, and there are specific EMG findings associated with OPIDN [29].

Toxicologic differential diagnosis for cholinergic toxicity includes nicotine, carbachol, methacholine, arecoline, bethanechol, pilocarpine, and Inocybe or Clitocybe mushrooms. Nontoxicologic diagnoses that may be mistaken for cholinergic toxicity include myasthenia gravis and Eaton–Lambert syndrome.

MANAGEMENT

Patients with all but the mildest symptoms should be admitted to an intensive care unit for careful observation and antidotal therapy as clinically indicated. The initial priorities are managing the patient's airway, breathing, and circulation. All personnel who are involved in the resuscitation and decontamination process should wear masks or respirators, aprons, and nitrile or butyl rubber gloves to avoid secondary contamination.

Most patients with severe cholinergic poisoning will require airway management and ventilatory assistance for respiratory

failure. Succinylcholine should be used with caution to aid intubation because prolonged (hours to days) paralysis may result [30]. A reasonable alternative is to use a double-dose of a nondepolarizing neuromuscular blocker (such as vecuronium) Airway and bronchial secretions are treated with atropine. The initial adult dose is 1 to 2 mg parenterally, which is doubled every 5 minutes (pediatric dose, 0.05 mg per kg) as needed until pulmonary secretions are controlled [31].

Initial resuscitation with IV fluids is needed because of significant gastrointestinal (GI) fluid losses Blood pressure support may require direct-acting pressors such as norepinephrine, phenylephrine, epinephrine and cardiac depression may require the use of dobutamine [2]. Patients should be treated with atropine (using the dosing scheme describe in the previous paragraph) until the systolic blood pressure is greater than 80 mm Hg and urine output exceeds 0.5 mL per kg per hour [31]. Electrical pacing is rarely needed to treat ventricular dysrhythmias. Potassium and magnesium should be normalized to minimize QTc prolongation.

Seizures should be treated with IV atropine and a benzodiazepine (diazepam, 0.2 to 0.4 mg per kg or an equivalent). Animal studies suggest that both atropine and benzodiazepine are efficacious [32]. Given the potential benefits of benzodiazepines in severe organophosphate poisonings to mitigate neuropsychiatric sequelae, it is reasonable to administer a benzodiazepine even if seizures are not apparent.

Decontamination can limit absorption and prevent reexposure. All of the patient's clothing should be removed and discarded, and the body should be thoroughly washed with mild soap and water. If the ingestion is recent, nasogastric suction can used to attempt to aspirate any product remaining in the stomach [33]. Although single and multidose charcoal did not change outcome in one trial [34], many of the subjects in this trial had long delays before treatment and it is possible that early treatment may limit toxicity. Dilute hypochlorite solution (household bleach) inactivates the organophosphorus ester and can be used to decontaminate equipment but should not be used on skin [35].

Antidotal therapy is comprised of two complementary agents, atropine and an oxime such as pralidoxime (North America, India, and Asia) or obidoxime (Europe and Middle East). Atropine is a competitive antagonist of acetylcholine at the muscarinic receptors but has no effect on muscle weakness or paralysis and does not affect the AChE regeneration rate. As noted above, atropine is primarily indicated for control of pulmonary secretions and bronchospasm. It has a secondary role in helping to control seizures and CNS manifestations of poisoning [36]. Careful titration of atropine to the individual patient is required, with frequent clinical reevaluation to prevent atropine toxicity [33]. Atropine therapy should be restarted at the first signs of cholinergic excess. A continuous atropine infusion may be necessary to stabilize the patient, after which the infusion can be titrated back while close observation is maintained. Most patients will respond to 3 to 5 mg per hour [33]. In general, higher doses of atropine are required during the first 24 hours with organophosphate pesticides than with nerve agents. Tachycardia is not a contraindication to atropine therapy; it may reflect hypoxia or sympathetic stimulation. Mydriasis may be an early response but is a poor marker for adequate atropinization. A common pitfall is inadequate atropine dosing during serious cholinergic agent overdoses. High doses of atropine are commonly needed for control of secretions. Daily doses in excess of 100 mg are occasionally required for several days [37]. Glycopyrrolate is an antimuscarinic agent that does not penetrate the CNS. It can be substituted for atropine when isolated peripheral cholinergic toxicity is present. The recommended dose is 0.05 mg per kg. One study suggested that a combination of atropine and glycopyrrolate may improve outcomes [38].

Pralidoxime (2-PAM) and obidoxime are nucleophilic oximes that regenerate AChE at muscarinic and nicotinic synapses by reversing the AChE active site phosphorylation. Although pralidoxime does not enter the CNS well, rapid improvement in coma or termination of seizures has been observed after pralidoxime administration [39]. The antidotal effect of atropine and oximes is synergistic.

Although oximes remain a standard therapy for organophosphate poisoning, recent studies have highlighted our limited understanding of their role. Although one recent randomized controlled trial showed a dramatic treatment effect with pralidoxime [40], a second trial found no benefit and a trend toward worse outcomes [41]. There are several possible explanations for these discrepant results, including differences in the lipophilicity, side chains (O′-dimethyl vs. O′-diethyl organophosphates), rate of aging, and interaction between inhibition/re-inhibition and spontaneous reactivation of the parent and oxime-bound compounds. Future studies will have to address these differences.

Although the optimal treatment protocol for pralidoxime is not known, there is consensus that many older protocols used insufficient doses [42]. Animal studies suggested that a serum concentration of 4 mg per mL were effective [43], and earlier pharmacokinetic studies suggested the use of 1 to 2 g IV pralidoxime followed by 1 g every 6 to 12 hours would produce a serum level of 4 mg per mL [44,45]. Subsequent studies in poisoned patients have shown that the amount of circulating inhibitor (parent or metabolite of the original organophosphate) determines the need for oxime [46]. Patients who have ingested massive amounts of an organophosphate may have prolonged high levels of circulating inhibitor for days after ingestion and the pralidoxime blood level of 4 mg per mL is too low to allow for continued reactivation of the acetylcholinesterase. Ideally, poisoned patients should be followed by serial evaluation of the ability to reactivate their cholinesterase in vitro [6]. Since this is not feasible for most patients, the following suggestions can be made. The World Health Organization recommends an initial pralidoxime dose of 30 mg per kg IV followed by 8 mg per kg per hour or alternatively, 30 mg per kg every 4 hours if a continuous infusion is not possible [42]. The appropriate dose of obidoxime 250 mg initially followed by 750 mg over 24 hours [47]. Muscle fasciculation and weakness should show a response within 60 minutes after dosing and the dose titrated upwards if the patient has breakthrough signs and symptoms. In mass casualty situations, the intramuscular route of administration may be more practical. The duration of therapy is based on clinical response and is usually 24 to 48 hours. Under ideal conditions, serum samples can be assayed for acetylcholinesterase reactability and this can be used to guide oxime therapy [48]. Some patients may require continuous treatment for greater than 1 week, depending on the body burden of organophosphate and reinhibition of reactivated acetylcholinesterase.

Although hemoperfusion can enhance the elimination of anticholinesterase agents [49], the availability of specific antidotes for organophosphates and the relatively short course of carbamate intoxications make this procedure unnecessary.

Carbamate poisonings are expected to have a good prognosis because the duration of serious signs and symptoms is limited. Severe organophosphate poisonings may require prolonged respiratory support, with its attendant complications. Death from acute organophosphate poisonings usually occurs within 24 hours in untreated cases, although exposures to fenthion and dimethoate may lead to death within 72 hours even if treated [2]. Aggressive respiratory management, timely antidotal therapy, and intensive supportive care are expected to improve morbidity and mortality. Recovery from OPIDN may be gradual or not at all. CNS anoxic sequelae have the worse prognosis and are not specific to

cholinesterase inhibitors but rather a consequence of prolonged hypoxia.

Toxicity of AChE Inhibitors Used to Treat Alzheimer's Disease

With the increasing use of AChE inhibitors to treat dementia, there has been an increasing number of exposures to these medications. Symptoms can range from general weakness [50] to salivation and GI effects [51] but are generally milder than pesticides. However, one case of deliberate ingestion of 288 mg of rivastigmine results in seizures, respiratory muscle weakness and bronchial secretions [52]. Muscarinic effects should be treated with atropine and one report has suggested that isolated CNS effects without peripheral muscarinic symptoms can be treated with pralidoxime alone [53].

NERVE AGENTS USED IN WARFARE

Since the Persian Gulf War and in the aftermath of the terrorist attacks of September 11, 2001, there has been increasing concern about the potential use of nerve agents such as GA (Tabun), GB (Sarin), GD (Soman), and VX. These chemicals are similar in structure and function to the organophosphate insecticides but have a much greater potency. Please see Chapter 214 for a complete discussion of this topic.

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CHAPTER 129 ■ COCAINE POISONING

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Cocaine (benzoylmethylecgonine) is an alkaloid compound derived from the South American plant *Erythroxylon coca*. Its use as an illicit drug of abuse has reached epidemic proportions. Thirty-four million US citizens have used cocaine at least once; 5.9 million have used cocaine in the past year; and 2.1 million have used cocaine in the past month [1]. Among drug-related emergency department visits, cocaine is the most commonly used illicit substance seen [2]. Of all drug-related emergency department visits in the United States, cocaine is involved in approximately 20% [2].

PHARMACOLOGY

The pharmacologic effects of cocaine are complex, and they include direct blockade of the fast sodium channels, increase in norepinephrine release for the adrenergic nerve terminals, interference with neuronal catecholamine reuptake, and increase in excitatory amino acid concentration in the central nervous system (CNS). Blockade of the fast sodium channels stabilizes axonal membranes, producing a local anesthetic-like effect and a type I antidysrhythmic effect on the myocardium. The increase in catecholamine levels produces a sympathomimetic effect. The result of increased excitatory amino acid concentration in the CNS is increased extracellular dopamine concentration.

Cocaine is well absorbed through the mucosa of the respiratory, gastrointestinal, and genitourinary tract, including less common routes of absorption such as the urethra, bladder, and vagina. The cocaine hydrochloride salt is the form most often abused nasally or parenterally. Crack cocaine and cocaine freebase are alkaloid forms of cocaine that are produced by an extraction process. These forms are heat stable, can be smoked, and are absorbed through the pulmonary system. When intravenously administered or inhaled, cocaine is rapidly distributed throughout the body and CNS, with peak effects in 3 to 5 minutes. With nasal insufflation, absorption peaks in 20 minutes.

Cocaine has a half-life of 0.5 to 1.5 hours. It is rapidly hydrolyzed to the inactive metabolites ecgonine methyl ester and benzoylecgonine, which account for 80% of cocaine metabolism. These compounds have half-lives of 4 to 8 hours, with effects similar to those of cocaine. Minor cocaine metabolites include ecgonine and norcocaine. Urinary toxicology screens for recreational drugs typically assess for the presence of benzoylecgonine, which is usually present for 48 to 72 hours after cocaine use [3].

Cocaine is frequently abused in combination with other drugs. In particular, ethanol is a frequent coingestant [2]. This may be a popular combination because ethanol antagonizes cocaine's stimulatory effects. The metabolism of cocaine in the presence of ethanol produces cocaethylene, which has additional cardiovascular and behavioral effects [4]. Cocaethylene and cocaine are similar with regard to behavioral effects. However, cocaethylene has been more likely to result in death in animal studies. Human studies demonstrate that cocaethylene produces milder subjective effects and similar hemodynamic effects when compared with cocaine. Cocaethylene also has a direct myocardial depressant effect [4].

Cocaine toxicity is due to an exaggeration of its pharmacologic effects, resulting in myriad consequences that have an impact on every organ system. The widespread effects of cocaine are related to its ability to stimulate the peripheral and central sympathetic nervous systems, in addition to local anesthetic-like effects. Cocaine-induced seizures are most likely due to excess catecholamine stimulation.

Cocaine causes vascular effects through multiple pathophysiologic mechanisms that have been best described in the heart [5–7]. These include arterial vasoconstriction, in situ thrombus formation, platelet activation, and inhibition of endogenous fibrinolysis. In addition, myocardial oxygen demand is increased by cocaine-induced tachycardia and hypertension [5–8]. The direct local anesthetic-like effect of cocaine or secondary cocaine-induced myocardial ischemia [5,9] may be responsible for cardiac conduction disturbances [9] and dysrhythmias.

CLINICAL PRESENTATION

Clinical manifestations of acute cocaine toxicity may occur in a number of different organ systems. Most severe cocaine-related toxicity and cocaine-related deaths are manifested by signs of sympathomimetic overdrive (e.g., tachycardia, hypertension, dilated pupils, and increased psychomotor activity). This increased psychomotor activity causes increased heat production and can lead to severe hyperthermia and rhabdomyolysis [10].

Cocaine-induced cardiovascular effects are common. Of cocaine-related emergency department visits, chest pain is the most common complaint. Although most of these patients do

not have serious underlying etiology, myocardial infarction due to cocaine is a well-established entity and needs to be excluded [11,12]. It occurs in 6% of patients presenting with cocaine-associated chest pain [13]. The risk of myocardial infarction is increased 24-fold in the hour after cocaine use. In patients aged 18 to 45 years, 25% of myocardial infarctions are attributed to cocaine use [14]. Cocaine-associated myocardial infarction typically occurs in patients aged 18 to 60 years without apparent massive cocaine exposure or without evidence of cocaine toxicity. Patients with cocaine-associated myocardial infarctions frequently have atypical chest pain or chest pain that is delayed hours to days after their most recent cocaine use [5,11].

Cardiac conduction disturbances (e.g., prolonged QRS and QTc) and cardiac dysrhythmias (e.g., sinus tachycardia, atrial fibrillation/flutter, supraventricular tachycardias, idioventricular rhythms, ventricular tachycardia, torsade de pointes, and ventricular fibrillation) may occur after cocaine use [15–17]. Aortic dissection and endocarditis associated with cocaine abuse are uncommon [18].

The neurologic effects of cocaine may be manifested in a number of ways. Altered mental status and euphoria are typically short lived and without serious sequelae. The stimulatory effects of cocaine can lead to seizures, cerebral infarction, intracerebral bleeding, subarachnoid hemorrhage, transient ischemic attacks, migraine-type headache syndromes, cerebral vasculitis, anterior spinal artery syndrome, and psychiatric manifestations [19–21]. Cocaine is associated with a sevenfold increased risk of stroke in women [22].

Cocaine-induced seizures are typically single, brief, generalized, self-limited, and not associated with permanent neurologic deficit. These seizures may occur in the presence or absence of concurrent structural disease, such as infarction or hemorrhage. Multiple or focal seizures are usually associated with concomitant drug use or an underlying seizure disorder [19].

Cocaine has a number of direct and indirect effects on the lungs, and they are associated with how the drug is used [23]. These effects include asthma exacerbations, pneumothorax, pneumomediastinum, noncardiogenic pulmonary edema, alveolar hemorrhage, pulmonary infarction, pulmonary artery hypertrophy, and acute respiratory failure [24,25]. Asthma exacerbations are more common with crack cocaine usage, most likely due to particulate by-products of combustion [26]. Inhalation of cocaine is typically associated with deep Valsalva maneuvers to maximize drug delivery and can cause pneumothorax, pneumomediastinum, and noncardiogenic pulmonary edema.

The intestinal vascular system is particularly sensitive to cocaine effects because the intestinal walls have a wide distribution of α-adrenergic receptors. Acute intestinal infarction has been associated with all routes of cocaine administration [27].

The most deadly gastrointestinal manifestation of cocaine usage is seen in the patient who presents after ingesting packets filled with cocaine. These patients have been termed *body packers* or *body stuffers*. Body packers are patients who swallow carefully prepared condom or latex packets filled with large quantities of highly purified cocaine for the purposes of smuggling this drug into the country. In contrast, body stuffers are typically "street" drug dealers who swallow packets of cocaine while fleeing the police. These packets were generally prepared for distribution to individual customers and not to protect the body stuffer from absorbing cocaine. It was previously thought that cocaine ingested orally was metabolized in the gastrointestinal track and did not lead to systemic toxicity. This is clearly not the case and toxicity can develop in body stuffers and packers from cocaine leaking out of the swallowed packets. The dosage of cocaine exposure in body stuffers is generally substantially less than that of a body packer. However, toxicity is more likely to occur in the setting of body stuffers. Although massive exposure to leakage from a condom or latex-filled packet of a body packer can occur, most body packers identified by airport immigration officers, do not develop clinical toxicity. However, any patient identified as a body packer who has developed any signs of systemic cocaine toxicity (tachycardia, hypertension, diaphoresis, etc.) can rapidly develop worsening symptoms including life-threatening ones. These patients, when identified, have a high potential for progressively worsening toxicity and mortality [28].

Premature atherosclerosis can develop in chronic cocaine users. Further, cocaine-induced left ventricular hypertrophy can lead to hypertrophic and eventually a dilated cardiomyopathy and congestive heart failure [5]. Cocaine-associated dilated cardiomyopathy appears to have a reversible component, and some patients have demonstrated improvement after cessation of cocaine use [5].

Chronic severe cocaine users can present with lethargy and a depressed mental status that is not attributable to any other etiology (diagnosis of exclusion), the "cocaine washout syndrome." This self-limited syndrome usually abates within 24 hours but can last for several days and is thought to result from excessive cocaine usage that depletes essential neurotransmitters [29].

Chronic inhalational use of cocaine does not appear to lead to long-term pulmonary effects. Spirometry and lung mechanics are typically normal even in heavy chronic users [30].

Chronic cocaine usage during pregnancy increases the chance for premature delivery and abruptio placentae [31]. Maternal cocaine usage is associated with low birth weight, small head circumference, developmental problems, and birth defects in the neonate [32–34]. Neonates exposed to cocaine in utero may develop cocaine withdrawal syndrome, which typically begins 24 to 48 hours after birth and is characterized by irritability, jitteriness, and poor eye contact.

DIAGNOSTIC EVALUATION

Patients manifesting cocaine toxicity should have a complete evaluation focusing on the history of cocaine use, signs and symptoms of sympathetic nervous system excess, and evaluation of specific organ system complaints. It is of paramount importance to determine whether signs and symptoms are due to cocaine itself, underlying structural abnormalities, or cocaine-induced structural abnormalities.

Friends or family of patients with altered mental status should be questioned about a history of cocaine usage and the events before presentation. Many patients deny cocaine use. Urine drug testing may be helpful in establishing recent cocaine use [35,36].

When the history is clear and symptoms are mild, laboratory evaluation is usually unnecessary. In contrast, if the patient manifests moderate or severe toxicity, routine laboratory evaluation should include a complete blood cell count, serum electrolytes, glucose, blood urea nitrogen, creatinine, creatine kinase (CK), cardiac marker determinations, arterial blood gas analysis, and urinalysis. Sympathetic excess may result in hyperglycemia and hypokalemia. Elevated CK is associated with rhabdomyolysis. Cardiac markers are elevated in myocardial infarction. However, false elevations of CK–MB fraction are common [12]. In the setting of an elevated absolute CK–MB, caution should be placed on the use of the CK–MB relative index, because it may be falsely low when there is concurrent myocardial infarction and rhabdomyolysis. Cardiac troponin I is the preferred method to distinguish true- from false-positive CK–MB determinations [12].

Chest radiography and electrocardiography (ECG) should be obtained in patients with chest pain or cardiovascular

complaints. The initial ECG is a less useful diagnostic tool than for patients with chest pain that is unrelated to cocaine. Many young cocaine-using patients have ST-segment elevation in the absence of acute myocardial infarction. This is due to early repolarization changes [15,16].

Observation for a 9- to 12-hour period is also a useful tool for the evaluation of patients presenting with cocaine-associated chest pain. Patients without new ischemic changes on ECG, a normal troponin test, and no cardiovascular complications during this observation (dysrhythmias, acute myocardial infarction or recurrent symptoms) can safely be sent home with follow up and planned outpatient workup [17,37]. Recent data also suggests that a strategy using coronary computerized angiographic tomography might identify patients safe for discharge in a slightly more rapid time frame [38].

A brief seizure temporally related to cocaine use in an otherwise healthy person should be evaluated with a head computed tomography (CT). Further workup in an otherwise asymptomatic patient may not be necessary [19]. Patients with concurrent headache, suspected subarachnoid hemorrhage, or other neurologic manifestations may necessitate lumbar puncture after head CT to rule out serious pathology. Patients who are suspected of body stuffing should be evaluated by abdominal radiographs and cavity searches (digital or visual examination of the rectum or vagina).

MANAGEMENT

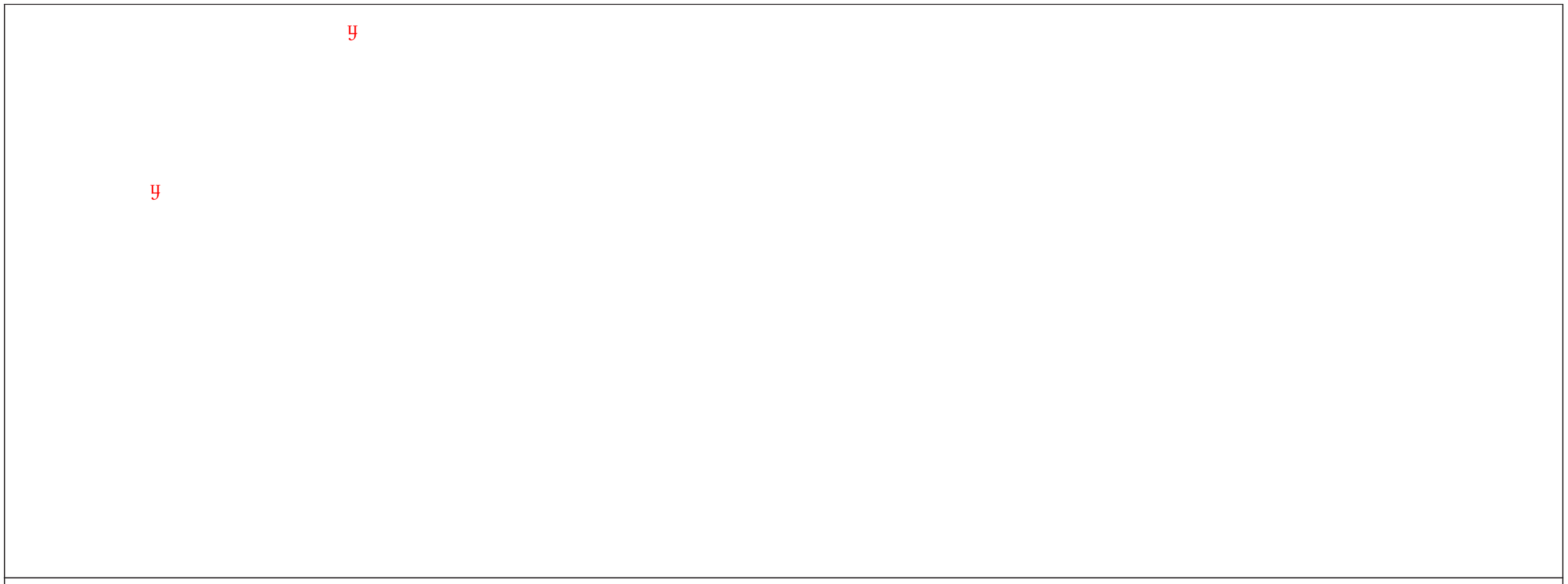
The initial management of cocaine-toxic patients should focus on airway, breathing, and circulation. Treatments are directed at a specific sign, symptom, or organ system affected and are summarized in Table 129.1.

Patients who present with sympathetic excess and psychomotor agitation are at risk for hyperthermia and rhabdomyolysis. Management should focus on lowering core body

TABLE 129.1

TREATMENT SUMMARY FOR COCAINE-RELATED MEDICAL CONDITIONS

Medical condition	Treatments
Cardiovascular	
Dysrhythmias	
Sinus tachycardia	Observation Oxygen Diazepam or lorazepam
Supraventricular tachycardia	Oxygen Diazepam or lorazepam Consider diltiazem, verapamil or adenosine If hemodynamically unstable: cardioversion
Ventricular dysrhythmias	Oxygen Diazepam or lorazepam Consider Sodium bicarbonate and/or lidocaine If hemodynamically unstable: defibrillation
Acute coronary syndrome	Oxygen Aspirin Diazepam or lorazepam Nitroglycerin Heparin For ST segment elevation (STEMI): Percutaneous intervention (angioplasty and stent placement) preferred. Consider fibrinolytic therapy. Consider morphine sulfate, phentolamine, verapamil or glycoprotein IIb/IIIa inhibitors
Hypertension	Observation Diazepam or lorazepam Consider nitroglycerin, phentolamine and nitroprusside
Pulmonary edema	Furosemide Nitroglycerin Consider morphine sulfate or phentolamine
Hyperthermia	Diazepam or lorazepam Cooling methods If agitated, consider paralysis and intubation
Neuropsychiatric	
Anxiety and agitation	Diazepam or lorazepam
Seizures	Diazepam or lorazepam Consider phenobarbital
Intracranial hemorrhage	Surgical consultation
Rhabdomyolysis	IV hydration Consider sodium bicarbonate or mannitol If in acute renal failure: hemodialysis
Cocaine washout syndrome	Supportive care
Body packers	Activated charcoal Whole-bowel irrigation Laparotomy or endoscopic retrieval



temperature, halting further muscle damage and heat production, and ensuring good urinary output. The primary agents used for muscle relaxation are benzodiazepines [11].

The use of antipsychotic agents for cocaine-induced neurobehavioral agitation is controversial [39]. In mild cases, antipsychotics may be useful. In cases of severe cocaine-induced agitation, few data exist on antipsychotics' safety and efficacy. In these cases, benzodiazepines are preferred and supranormal cumulative doses may be necessary. Core body temperatures may be highly elevated. This should be treated aggressively with iced water baths or cool water mist with fans. Some cases of severe muscle overactivity may require general anesthesia with nondepolarizing neuromuscular blockade. Succinylcholine, a depolarizing neuromuscular-blocking agent, may increase the risk of hyperkalemia in the setting of severe cocaine-induced rhabdomyolysis. In addition, plasma cholinesterase is responsible for the metabolism of both succinylcholine and cocaine. When these two agents are used simultaneously, prolonged clinical effects of either or both agents might result. Therefore, nondepolarizing agents are preferred.

Patients with severe hypertension can usually be safely treated with benzodiazepines. When benzodiazepines are not effective, nitroglycerin, nitroprusside, or phentolamine can be used. Beta-blockers are contraindicated. Their use in this setting can lead to unopposed alpha stimulation with paradoxic exacerbation of hypertension and worsening coronary vasoconstriction [40,41].

Patients with chest pain and suspected cocaine-induced ischemia or myocardial infarction should be treated with aspirin, benzodiazepines, and nitroglycerin as first-line agents. Benzodiazepines decrease the central stimulatory effects of cocaine, thereby indirectly reducing its cardiovascular toxicity [11]. Benzodiazepines have been shown to have a comparable and possibly an additive effect to nitroglycerin with respect to chest pain resolution and hemodynamic and cardiac functional parameters (cardiac output) for patients with cocaine-associated chest pain [42,43] (Table 129.2). Weight-adjusted unfractionated heparin or enoxaparin would be reasonable to use in patients with documented ischemia. Patients who do not respond to these initial therapies can be treated with phentolamine or calcium channel blocking agents [44,45]. The International Guidelines for Emergency Cardiovascular Care recommend α-adrenergic antagonists (phentolamine) for the treatment of cocaine-associated acute coronary syndrome [46]. Beta-blockers are contraindicated, as they can exacerbate cocaine-induced coronary artery vasoconstriction [40].

Primary reperfusion therapy is best done with percutaneous interventions, when available [47]. Fibrinolytic therapy in this setting is somewhat controversial. The mortality from cocaine-associated myocardial infarction is low. Patients with cocaine-associated chest pain have a high prevalence of "false-positive ST-segment elevations," up to 43% in one study [48]. Therefore, treatment of all patients with cocaine-associated chest pain who meet standard ECG thrombolysis in myocardial infarction criteria would result in fibrinolytic administration to more patients without acute myocardial infarction than with acute myocardial infarction.

Supraventricular dysrhythmias may be difficult to treat. Initially, benzodiazepines should be administered. Adenosine can be given, but its effects may be temporary. Use of calcium channel blockers in association with benzodiazepines appears to be most beneficial. Beta-blockers should be avoided [46].

Ventricular dysrhythmias should be managed with benzodiazepines, lidocaine, or sodium bicarbonate [46]. Bicarbonate is preferred in patients with QRS widening and ventricular dysrhythmias that occur soon after cocaine use. In this setting, the dysrhythmias are presumably related to sodium channel blocking effects of cocaine. Lidocaine can be used when dysrhythmias appear to be related to cocaine-induced ischemia [9,46].

Seizures should be treated with benzodiazepines and phenobarbital. Phenytoin is not recommended in cases associated with cocaine. Although no studies have compared barbiturates to phenytoin for control of cocaine-induced seizures, barbiturates are theoretically preferable because they also produce CNS sedation and are generally more effective for toxin-induced convulsions. If these agents are not rapidly effective, nondepolarizing neuromuscular blockade and general anesthesia are indicated.

Patients with cerebrovascular complications or focal neurologic findings should be managed as usual. However, the utility of fibrinolytic agents in cocaine-associated cerebrovascular infarction is unknown.

Cocaine body stuffers who are asymptomatic should be given activated charcoal [49]. Whole-bowel irrigation with subsequent radiologic verification of passage of all drug-filled containers should be considered [28]. Body stuffers who manifest clinical signs of toxicity should be treated similarly to other cocaine-intoxicated patients. Body packers who develop any signs of cocaine toxicity, need to be identified as quickly as possible and treated very aggressively. These individuals have a high likelihood of developing worsening toxicity and life-threatening symptomatology. Initial use of activated charcoal and surgical removal of ruptured cocaine packets is warranted in almost all cases and can be life saving [29].

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CHAPTER 130 ■ CORROSIVE POISONING

ROBERT P. DOWSETT AND CHRISTOPHER H. LINDEN

Initially referring to acids, the term *corrosives* is now used synonymously with *caustics*, a term originally applied to alkalis. In solution, acids and bases donate or accept a proton altering the hydrogen ion concentration. This is measured as pH, the negative logarithm of the H^+ ion concentration (M/L) Water, at 25°C, has a pH of 7 and is considered neutral. Solutions with a pH of less than 2 or greater than 12 are considered strongly acidic or basic. The pH levels of some common solutions are listed in Table 130.1.

Corrosives cause injury by reacting with organic molecules and disrupting cell membranes. They also cause thermal burns if heat is generated by dissolution and neutralization reactions. Reactions between strong acids and strong bases are usually highly exothermic. Metallic lithium, sodium, potassium, some aluminum and lithium salts, and titanium tetrachloride react violently when placed in water, producing large amounts of heat. Chlorine reacts with water in an exothermic reaction to form hydrochloric and hypochlorous acids, elemental chlorine, and free oxygen radicals. Similar reactions occur with bromine. Ammonia combines with water to form ammonium hydroxide in a reaction that liberates heat; the hydroxide formed is then responsible for corrosive effects. Nitrogen dioxide reacts with water to release heat and produce nitric and nitrous acid. Hydrogen peroxide liberates oxygen on contact with water.

The mixing of chemicals can result in reactions that liberate caustic gases. Mixing ammonia with hypochlorite (household bleach) generates chloramine gases (NH_2Cl and $NHCl_2$), which are highly irritating to mucosal epithelia. Combining bleach with acid (acid toilet bowl or drain cleaners) produces chlorine gas. A number of metallic compounds react with acids, resulting in the liberation of potentially explosive hydrogen gas. Hydrogen sulfide and sulfur oxide gas result from the action of acids on sulfur-containing compounds such as orthopedic plaster casting material in sink drains [1]. Zinc hydroxide, present in soldering flux, is corrosive in an acidic environment such as the stomach [2].

TABLE 130.1

APPROXIMATE pH OF COMMON SOLUTIONS

Solution	pH
1.0 M hydrochloric acid	0
1 M hydrochloric acid solution	0
1 M nitric acid solution	0
0.1 M sulfuric acid	0.96
Battery acid (1% solution)	1.4
Gastric juice	1.2–3.0
Lemon juice	2
Domestic toilet cleaner (1%)	2.0
1 M acetic acid solution	2.37
1 M carbonic acid	5.7
Rain water	6.5
Water (pure, at 25°C)	7.0
Bleach (1% solution)	9.5–10.2
Automatic dishwasher detergents	10.4–13.0
Laundry detergents	11.6–12.6
Domestic ammonium cleaners	11.9–12.4
Ammonia 10%	12.5
Oven cleaner	13
Drain cleaner	13.3–14.0
1.0 M potassium hydroxide	14
1.0 M NaOH	14
Saturated ammonia solution	15

During 2007, 147,703 exposures to corrosive chemicals were reported by U.S. poison centers; actual exposures are estimated to be several times greater [3]. Lethal exposures constituted 1.9% of all reported deaths due to poisoning [3]. Exposures to chemicals accounted for 7.6% of poisonings in children younger than 6 years of age. Only a few of these cases resulted in serious injury, with only three deaths. Adults, usually by deliberate intent, ingest a larger amount of corrosive [4]. Deaths most commonly result from intentional exposure to drain cleaners and acidic cleaners [3].

Concentrated lye (sodium or potassium hydroxide) solutions used for laundering and plumbing purposes caused most of the serious injuries due to corrosive ingestions before 1970 [5]. Currently available liquid lye drain cleaners are less concentrated (less than 10%) but are still responsible for the largest number of severe gastrointestinal injuries; however, acid bowl cleaners now account for almost as many deaths [3]. Severe alkali injuries can result from the ingestion of powdered automatic dishwasher detergents and oven cleaners [6,7]. Household ammonia and bleaches, and hydrogen peroxide solutions are in general much less potent than industrial ones but can cause significant injury if ingested in large amounts [4,6].

PATHOPHYSIOLOGY

Alkalis cause liquefaction necrosis, a process resulting from the saponification of fats, dissolution of proteins, and emulsification of lipid membranes. The resultant tissue softening and sloughing may allow the alkali to penetrate to deeper levels. Tissue injury progresses rapidly over the first few minutes but can continue for several hours [8]. Over the ensuing 4 days, bacterial infection and inflammation cause additional injury. Granulation tissue then develops, but collagen deposition may not begin until the second week. The tensile strength of healing tissue is lowest during the first 2 weeks. Epithelial repair may take weeks to months. Scar retraction begins in the third week and continues for months.

Acid burns are characterized by coagulation necrosis. Protein is denatured, resulting in the formation of a firm eschar [9]. The release of heat is typically higher than for alkali reactions [10]. Subsequent responses are similar to those seen with alkalis.

Hydrocarbons can produce injury by dissolving lipids in cell membranes and coagulating proteins. Significant damage may occur with ingestion or after prolonged dermal contact [11]. Ingestion of a toluene containing glue can cause caused corrosive esophagitis [12]

Alkaline solutions with a pH of greater than 12.5 are likely to cause mucosal ulceration, with deeper tissue necrosis resulting if the pH approaches 14 [13]. However, solutions with a pH of less than 12.5 can still cause significant injury, and solutions of different chemicals but the same pH produce different degrees of tissue damage [13].

The physical state of a chemical also influences its toxicity. Corrosives that are gases at room temperature primarily affect the skin, eyes, and airways. Saturated acid solutions may liberate significant amounts of acid fumes, particularly if heated. Solid compounds tend to produce highly concentrated solutions on contact with body fluids and cause more severe injuries [14]. Solutions with a high viscosity tend to cause deeper burns [13].

Most systemic effects that occur after exposure to corrosives are secondary to inflammation, acidosis, infection, and necrosis [15]. Fluid and electrolyte shifts occur, resulting in hypovolemia, acidosis, and organ failure. Some chemicals, such as phenol, hydrazine, and chromic acid, can be absorbed after dermal exposure or ingestion and cause systemic toxicity [16,17].

CLINICAL MANIFESTATIONS

Chemical burns to the eye range from irritation to severe and permanent damage [18]. Eye pain, blepharospasm, conjunctival hemorrhages, and chemosis are seen in all grades of injury. Decreased visual acuity may result from excessive tearing, corneal edema and ulceration, anterior chamber clouding, or lens opacities. Roper-Hall's classification of injury predicts severity of subsequent vision loss [19] (Table 130.2).

TABLE 130.2

GRADING OF SEVERITY OF OCULAR CHEMICAL BURNS

Grade	Cornea	Limbal ischemia	Prognosis
I	Epithelial loss	None	Good
II	Stromal haze, iris details visible	$< 1/3$ of vessels affected	Good
III	Total epithelial loss, iris details obscured	$1/3$–$1/2$ of vessels affected	Doubtful, vision reduced
IV	Opaque, no view of iris or pupil	$> 1/2$ of vessels affected	Poor

Severe burns can result in increased intraocular pressure, anterior chamber clouding, lens opacities, and perforation of the globe [18]. Severity can be assessed by the extent of ischemia of conjunctival vessels at the limbus of the eye. If more than half of these vessels are obliterated, the prognosis is poor [19].

Significant differences exist between thermal and chemical burns of the skin. Although pain usually occurs immediately, it may be delayed several hours after corrosive exposure [20]. Assessing the depth of dermal injury can be difficult. Chemical burns rarely blister, and the affected skin is usually dark, insensate, and firmly attached regardless of the burn depth [21]. Healing usually takes longer than for thermal burns.

Some chemical warfare agents cause severe dermal injury. Sulfur mustard, the most common antipersonnel agent used, and lewisite (chlorovinylarsine dichloride) are potent alkylating agents, resulting in severe vesiculation of the skin 4 to 12 hours after exposure. Phosgene oxide has a similar action, but its effects are almost immediate. Respiratory burns are nearly always associated with sulfur mustard exposure [22]. White phosphorus is used in incendiary devices and in the manufacture of fertilizers and insecticides. It ignites spontaneously when exposed to air.

Ingested corrosives typically injure the oropharynx, esophagus, and stomach but may cause damage as distal as the proximal jejunum [23,24]. Areas most commonly affected are those of anatomic narrowing: the cricopharyngeal area, diaphragmatic esophagus, and antrum and pylorus of the stomach [23]. Multiple sites are affected in up to 80% of patients [24]. Esophageal lesions are seen predominantly in the lower half, and gastric burns are usually most severe in the antrum [24]. In the presence of food, gastric injuries tend to be less severe and involve the lesser curve and pylorus [10]. Vomiting is associated with a higher incidence of severe esophageal injuries [25].

Ingestion of alkali is associated with a higher incidence and severity of esophageal lesions than ingestion of acid, which typically causes stomach injury although this is not a consistent finding [4,25]. Alkaline agents have little taste, but acids are extremely bitter and more likely to be expelled if accidentally ingested.

Alkaline solids may adhere to mucosa of the oropharynx and cause oral pain that limits the quantity swallowed, thus sparing the esophagus [26]. If alkaline solids are swallowed, severe upper esophageal burns are seen [27]. Shallow ulcers may result when tablets become lodged in the esophagus (pill esophagitis). Hemorrhage and stricture formation may occur after esophageal impaction of potassium chloride, iron, quinidine, etidronate, antibiotics, and anti-inflammatory agents [28].

Common symptoms from corrosive ingestion are oropharyngeal pain, dysphagia, abdominal pain, vomiting, and drooling [29]. Less commonly, stridor, hoarseness, hematemesis, and melena are seen. Patients who are asymptomatic are unlikely to have significant injuries, although this may be difficult to assess in children who may appear to have no or minimal symptoms [29]. Vomiting, drooling, and stridor appear to be predictive of more severe injuries [29].

The absence of burns in the oropharynx does not exclude burns further along the gastrointestinal tract, and it is not predictive of less severe distal injuries [29]. Patients with laryngeal burns have a greater incidence and severity of esophageal lesions [25].

Hemorrhage, perforation, and fistula formation may occur in patients with full-thickness esophageal necrosis [24]. Untreated, perforations rapidly progress to septic shock, organ failure, and death. Some gastric perforations may become walled to form an abscess around the liver or in the lesser sac.

Severe gastric burns may extend to adjacent organs [30]. Perforation of the anterior esophageal wall may lead to formation of a tracheoesophageal fistula and tracheobronchial necrosis [31,32]. Tracheoesophageal–aortic and aortoesophageal fistulas, rare and uniformly fatal complications, are suggested by hemoptysis or hematemesis, which develops into torrential bleeding [33,34].

Burns to the larynx occur in up to 50% of patients and are the most common cause of respiratory distress [25]. Typically, the epiglottis and aryepiglottic folds are edematous, ulcerated, or necrotic. The absence of respiratory symptoms on presentation does not exclude the presence of laryngeal burns that may eventually require intubation [25]. Respiratory distress may also be due to the aspiration of corrosives [35].

Esophageal strictures develop in up to 70% of burns that result in deep ulceration, whether discrete or circumferential, and nearly all burns resulting in deep necrosis [24]. Strictures do not develop after superficial mucosal ulceration [35]. Strictures may become symptomatic as early as the end of the second week; half develop during initial hospitalization, and 80% are evident within 2 months [36]. Those that develop early often progress rapidly and require urgent intervention. Gastric outlet strictures may also occur, but only 40% become symptomatic [24]. Strictures can develop in the mouth and pharynx [25].

Esophageal pseudodiverticulum may occur in patients with esophageal stricture as early as 1 week after corrosive ingestions. It appears to result from incomplete destruction of the esophageal wall and usually resolves with dilation of associated strictures [37].

Deaths that occur are in patients who have extensive necrosis in the upper gastrointestinal tract. Sepsis secondary to perforation is the most common cause of death; severe hemorrhage or aspiration may also contribute [24].

Esophageal carcinoma, usually squamous cell, is a well-documented complication of alkali burns [38]. It occurs most commonly at the level of the tracheal bifurcation and is estimated to occur 1,000 times more frequently in patients who have had corrosive injuries than in the general population. Symptoms can develop 22 to 81 years after the initial insult.

Systemic toxicity has occurred with burns caused by arsenic and other heavy metals, cyanide, acetic acid, formic acid, fluoride, hydrazine, hydrochloric acid, nitrates, sulfuric acid, and phosphoric acid [39–43]. Severe acid burns may be accompanied by a metabolic acidosis and hypotension. The anion gap is usually elevated, although a hyperchloremic acidosis may be seen in hydrochloric acid and ammonium chloride ingestion. After hydrochloric acid ingestion, cardiovascular collapse is the most common cause of early death; myocardial infarction has occurred after large ingestions. Other findings associated with severe acid injuries include hemolysis, hemoglobinuria, nephrotoxicity, and pulmonary edema [40,41,43].

Acute hemolysis, hyperkalemia, hypoxia, and cardiorespiratory arrest have occurred after the use of dialysis equipment and syringes sterilized with bleach [44]. Vascular oxygen embolization can occur after the ingestion of concentrated hydrogen peroxide [45]

DIAGNOSTIC EVALUATION

Resuscitation and decontamination should take priority over completing a detailed history and physical examination. Medical staff should wear protective clothing to avoid becoming secondary casualties. The duration of exposure, symptoms, and details of prehospital treatment should be noted. Identification of the compounds involved and any measures required for their safe handling can be established by a number of means: Container labeling, material safety data sheets and safety officers in cases of workplace exposure, fire department hazardous materials units, and regional poison information centers. Measuring the pH of a product may be helpful.

If the exposure is the result of an industrial or transportation accident, the patient should be evaluated for traumatic injuries. Suicidal patients should be evaluated for other possible toxic exposures (e.g., ingestion of alcohol or medications). Pulmonary exposures should be evaluated as outlined in Chapter 64.

After decontamination, assessment of eye exposures should include measurement of visual acuity and conjunctival pH and a slit-lamp examination. Chemosis, conjunctival hemorrhages, corneal epithelial defects, stromal opacification, and loss of limbic vessels should be noted. If injury to the anterior chamber is suspected, intraocular pressure should be measured.

Assessment of dermal injury is similar to that for thermal burns. Location, size, color, texture, and neurovascular status should be noted. If the affected area is greater than 15% of total body surface area or if systemic toxicity is possible, a complete physical examination with appropriate monitoring and laboratory testing should be performed.

With ingestions, the ability to swallow secretions and findings on examination of the oropharynx, neck, chest, and abdomen should be noted. Particular attention should be given to assessing the patency of the airway. Patients with signs and symptoms suggestive of significant injuries should have an electrocardiogram, arterial blood gas analysis, complete blood cell count, type and cross-match, coagulation profile, and biochemistry testing, including electrolytes, glucose, and liver and renal function. Radiologic studies should include a chest radiograph and an upright abdominal film. Upper gastrointestinal endoscopy should be performed in symptomatic patients or those with visible burns in the mouth or throat. Although the absence of symptoms or signs does not preclude the presence of gastrointestinal burns, in patients with accidental ingestions, such injuries are always of a minor nature and endoscopy is not necessary [23]. Minor symptoms or grade I visible burns following the accidental ingestion of substances shown to have low toxicity, such as sodium hypochlorite household bleach (less than 10% solution) and hair relaxer gel, do not necessarily require endoscopy, as significant injuries are rare in this setting [46–48]. However, endoscopy is still recommended if excessive drooling or dysphagia or significant mucosal burns occur after ingestion of these products or if there is doubt about the exact composition of the ingested substance [46,47]. In contrast, in those with ingestions of strong acids or bases, significant injuries may be present in the absence of clinical findings, and endoscopy is indicated. The optimal timing of endoscopy appears to be 6 to 24 hours after exposure. Because injuries may progress over several hours, endoscopy performed earlier may not detect the full extent of injury and therefore may need to be repeated [2]. If performed later, the risk of perforation is increased [24].

In the past, it was recommended that the endoscope not be passed beyond the first circumferential or full-thickness lesion because of the risk of iatrogenic perforation [48]. This complication was a significant problem in the days when rigid endoscopes were used. It is extremely rare with flexible endoscopy. Not examining beyond the first significant lesion results in failure to detect more distal lesions of the stomach or duodenum [49]. Flexible endoscopy, preferably using a small-diameter (e.g., pediatric) endoscope, of the entire upper gastrointestinal tract is safe and usually well tolerated [24]. The endoscope should be advanced across the cricopharynx under direct vision to assess for the presence of laryngeal burns [24]. If laryngeal edema or ulceration is noted, the airway should be intubated before endoscopy is continued. Examination should be done gently with minimal air insufflation, avoiding retroversion or retroflexion, and the procedure terminated if the endoscope cannot be easily passed through a narrowed area. Therapeutic dilation of the esophagus on initial endoscopy carries a high risk of perforation and should be avoided [23]. It should also be avoided during the subacute phase (5 to 15 days after ingestion), when the tensile strength of tissues is lowest [24].

TABLE 130.3

EXAMPLES OF CLASSIFICATIONS FOR GRADING SEVERITY OF GASTROINTESTINAL CORROSIVE INJURY

Grade I	Mucosal inflammation
Grade II	A. Hemorrhages, erosions, and superficial ulceration
	B. Deep discrete or circumferential ulceration
Grade III	A. Small, scattered areas of necrosis
	B. Extensive necrosis involving the whole esophagus
First degree	Mucosal inflammation, edema, or superficial sloughing
Second degree	Damage extends to all layers of, but not through, the esophagus
Third degree	Ulceration through to periesophageal tissues

A number of different systems for grading gastrointestinal burns have been proposed [23,24]. Some parallel grading systems used for thermal skin burns; others differentiate several levels of ulceration and necrosis (Table 130.3). The important findings are depth of ulceration and presence of necrosis. Injuries that consist only of mucosal inflammation or superficial ulceration and do not involve the muscularis are not at risk for stricture formation [24]. Patients with full-thickness circumferential burns and extensive necrosis are at high risk for perforation and stricture formation. Deep ulceration, whether transmural or not, and discrete areas of necrosis can sometimes lead to stricture formation.

Contrast esophagography is less sensitive than endoscopy in visualizing ulceration but has a role in the detection of suspected perforation [50]. A water-soluble contrast agent should be used. Cineesophagography can detect esophageal motility disorders, the pattern of which may predict the likelihood of stricture formation. Strictures can be expected to develop in all patients with an atonic dilated or rigid esophagus and in some individuals with abnormal, uncoordinated contractions [51]. Endoscopic ultrasonography can accurately grade corrosive injuries and predict complications [52]. Esophageal motility studies may predict the risk of stricture formation in those patients with no peristaltic response; these motility abnormalities persist for at least 3 months [53].

Evaluation of patients with symptoms and signs of systemic toxicity should include routine monitoring and ancillary testing. The extent and type of testing depend on the nature and severity of clinical abnormalities and the chemical involved. Patients with significant exposure to some phenols (e.g., nitrophenol and pentachlorophenol) and to hydrazine should have methemoglobin level determination.

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Advanced life support measures should be instituted as appropriate. Decontamination is the next priority; procedures are specific to the route of exposure. Treatment of systemic poisoning is primarily supportive; in some cases, antidotal therapy may also be necessary.

Irrigation should be performed immediately for eye exposures. The procedure is described in Chapter 117. The persistence of eye pain despite irrigation for at least 15 minutes indicates significant injury or incomplete decontamination. Failure

to irrigate the eye adequately or remove particles after chemical exposure is associated with chronic complications [54]. Up to one third of patients with lime burns still have particles present in the eye on presentation [54]. All cases in which injury is detected or symptoms persist require ophthalmologic evaluation. Management may consist of topical antibiotics, mydriatics, steroids, and eye patching. The role of neutralization of chemical burns is currently under investigation. Ascorbic acid had been used to treat alkali burns, but its effectiveness has not been well studied, and it cannot be recommended [18].

The initial treatment of dermal exposure is prompt irrigation with copious amounts of water for at least 15 minutes for acid exposures and 30 minutes for alkali exposures (see Chapter 119). Longer irrigation is recommended for alkalis because they have detergent properties [20]. Although tissue neutralization occurs within 10 minutes with acids and 1 hour with alkalis in experimental studies, delayed irrigation may be beneficial [55]. Clothes act as a reservoir, and failure to remove them may result in full-thickness burns developing from even mildly corrosive chemicals [20]. Neutralization has been used [56], but because data on its efficacy are lacking, such therapy cannot be recommended.

Water irrigation may sometimes be dangerous or ineffective. Metallic lithium, sodium, potassium and cesium, titanium tetrachloride, and organic salts of lithium and aluminum react violently with water; burns caused by these agents should be inspected closely and any particles removed and placed in an anhydrous solution (oil) before the area is irrigated. Alternatively, the area can be wiped with a dry cloth to remove particles and the skin then deluged with water to dissipate any heat. Phenol is not water soluble, and dilution with water may aid its penetration into tissues, increasing systemic absorption [16]. Soaking experimental phenol burns with isopropyl alcohol or polyethylene glycol in mineral oil is superior to rinsing with water [57]. Isopropyl alcohol and polyethylene glycol may be absorbed by burns, and their use should be followed by liberal washing with water. Ready-mixed concrete can be easily removed from skin by soaking or irrigating with 50% dextrose in water [58].

Application of a copper sulfate solution has been suggested to assist in identification and neutralization of white phosphorus particles on the skin, but systemic absorption of copper sulfate can result in massive hemolysis with acute renal failure and death [59]. The use of a Wood's lamp to detect fluorescent phosphorus particles is safer [16]. Such burns should be kept wet because phosphorus ignites in dry air. Because sulfur mustard is poorly water soluble, a mild detergent should be used for its removal. Military decontamination kits contain chloramine wipes, which inactivates sulfur mustard [60]. British antilewisite, or dimercaprol, is an effective chelator of lewisite and can be applied topically to the skin or eye [22].

Patients with second- or third-degree skin burns should be referred to a surgeon. Definitive management is the same as for thermal burns, although more aggressive use of early débridement and grafting has been suggested [21].

Despite the rapidity of tissue injury following ingestion, decontamination should be considered. Rinsing with water or saline is recommended for mouth exposures. Dilution by drinking up to 250 mL (120 mL for a child) water or milk is recommended for particulate ingestion, because the corrosive may adhere to the esophageal wall. Although this procedure exposes the stomach to the corrosive agent, it further dilutes the substance. As the efficacy of dilution is greatest if performed within 5 minutes of exposure and declines rapidly thereafter, it is reasonable to use any drinkable beverage, except carbonated ones, if water or milk is not immediately available. The role of dilution for liquid ingestion is less clear, but it is usually recommended. It may, however, promote emesis and may not be effective in limiting tissue damage unless undertaken within minutes of injury. Emesis is contraindicated because of the risk of aspiration and its association with an increased severity of esophageal and laryngeal burns [25].

The administration of weak acids or bases can neutralize, as well as dilute, ingested corrosives [61]. Although weak acids are more effective than milk or water in neutralizing the pH, neutralization, which is accompanied by the production of heat, could lead to thermal injury in addition to corrosive effects. The heat generated by in vitro neutralization is small (less than 3°C) for liquid alkali but may be greater for solid forms [61]. The benefit of such therapy is unknown and not recommended [62].

Using a nasogastric tube for gastric aspiration, dilution, or lavage is another subject of debate [9]. Esophageal perforation is a potential complication, but no cases of nasogastric tube perforation have been reported. Placement of a gastric tube with fluoroscopic or endoscopic guidance has been suggested, but the blind, gentle introduction of a small-bore tube in a cooperative patient, particularly for an ingested acid, also appears to be safe [23]. If inserted, the tube should be firmly taped in place to avoid motion. Gastric contents should be aspirated. Dilution or lavage with small aliquots (120 to 250 mL) of water can then be performed.

Activated charcoal does not adsorb inorganic acids or alkali. In addition, because it interferes with endoscopic evaluation, unless a corrosive that has significant systemic toxicity and is known to be bound by activated charcoal has been ingested, this agent should be avoided. Symptomatic patients should otherwise be given nothing by mouth before endoscopy.

Corticosteroids have been used to reduce the incidence and severity of esophageal strictures after alkali burns. Such therapy is based on studies showing a decrease stricture formation in animals pretreated with steroids [63]. Because strictures do not develop in patients with first-degree esophageal burns, steroids are not indicated in those with such findings [64]. Similarly, steroids do not appear to influence the development of esophageal strictures after extensive deep ulceration or necrosis [64], and hence they are not recommended in patients with these injuries. Studies on the efficacy of steroids in patients with injuries of moderate severity have yielded conflicting results (Table 130.4). Most have been retrospective and poorly controlled [65–67]. Three analyses of pooled data from retrospective and prospective studies concluded a lower incidence of stricture formation with steroids in one study, but no difference in the other two [68–70]. There have been three prospective controlled studies of steroid use [71–73]. Two studies came to different conclusions; one showing a benefit with steroids, the other not [71,72] A criticism of the negative study was the delay to commencing steroids [74]. In an unpublished prospective randomized controlled trial of 362 patients, steroids did not show a benefit (73).

If steroids are administered, the recommended dose is 1 to 2 mg per kg per day prednisolone or methylprednisolone for 3 weeks followed by gradual tapering [74]. One comparative study suggested improved burn healing and reduced the need for dilatations with dexamethasone (1 mg per kg per day) compared with prednisolone (2 mg per kg per day) [75]. To approximate experimental conditions showing a beneficial effect, the initial dose of steroids should be given on presentation. Active bleeding and perforation are contraindications to steroid use.

Prophylactic antibiotics have also been advocated for patients with significant gastrointestinal injuries. Their benefits have not been studied in humans, and opinions differ as to their value. Controlled animal experiments have shown a combination of steroids and antibiotics to give the best outcome with respect to stricture formation and mortality [76] and suggest that a broad-spectrum antibiotic (e.g., a second-generation

TABLE 130.4

RESULTS OF CONTROLLED TRIALS OF STEROIDS FOR ESOPHAGEAL STRICTURES FOLLOWING CORROSIVE ESOPHAGEAL BURNS

Intervention	Year	Study	No. of patients	Findings	Reference
Prednisolone 25 mg 6 hourly (children 1.5 mg/kg/d for 2 weeks then tapered	1970	Retrospective controlled trial	21	Esophageal stricture rate: 27% in study group; 0% in controls	[64]
Methylprednisolone 125 mg IM, two doses 6 hours apart, then 40 mg 6 hourly for 5 days followed by reducing Depo-Medrol until healed	1980	Prospective randomized controlled trial	20	Esophageal stricture rate: 22% in study group; 36% in controls	[72]
Prednisolone 2 mg/kg/d IV until oral intake: 2.5 mg/kg/d for 21 days	1990	Prospective randomized controlled trial	25	Esophageal stricture rate: 7% in study group; 0% in controls	[71]
Steroid (not specified) 2 mg/kg/d (max. 30 mg/d) for 3 weeks	2005	Prospective randomized controlled trial	223	Esophageal stricture rate: 12% in study group; 19% in controls (NS)	[73]

cephalosporin) should be administered, particularly in those treated with steroids.

If initiated, the decision to continue or cease steroid and antibiotic therapy should be based on endoscopic findings. Patients with no injury or mucosal inflammation or small areas of superficial ulceration are not at risk for strictures or perforation and require supportive therapy only. Symptomatic relief can be provided with antacids, sucralfate, histamine-2–blockers (H_2-blockers), or analgesics. Patients with persistent symptoms or inconclusive findings on endoscopy should be admitted for observation. If symptoms persist, endoscopy should be repeated. Patients can commence oral fluids when they are able to swallow their own secretions. They can be discharged when tolerating oral fluids.

Patients with deep discrete ulcerations, circumferential or extensive superficial ulcerations, or small isolated areas of necrosis are at risk for stricture formation and should be given nothing by mouth. Fluids, analgesics, and H_2-blockers should be administered parenterally. Intravenous steroids and antibiotics should also be considered in those with alkali burns. Patients with deep transmural ulceration or necrosis are at risk for perforation as well as stricture formation. Although the use of steroids in this group is potentially hazardous and not recommended, antibiotics should be given along with other supportive measures. Hyperalimentation, either parenteral or by jejunostomy feeding tube, may be required.

Surgical exploration is indicated if perforation or penetration into surrounding tissues is suspected by findings such as fever, progressive abdominal or chest pain, hypotension, or signs of peritonitis or proved by endoscopic or radiographic findings. Tracheoesophageal fistulas are usually fatal unless recognized early and repaired, although one case reported successful conservative treatment [32]. Laparotomy and early excision have been suggested for patients with extensive full-thickness necrosis, but an advantage of this approach over more conservative treatment is not clear [77]. The mortality for patients who have major emergency surgery is 9% to 66% [77,78].

Stricture formation is usually treated with endoscopic dilatation beginning 3 to 4 weeks after ingestion. An average of eight sessions is required, but recurrence is common in the first 12 months [79]. In a group of 195 patients with corrosive-induced esophageal strictures, the risk of perforation for each dilatation session was 1.3%, but, because of the requirement for multiple dilations, the risk per patient was 17% [79]. Perforations were most likely to occur during the first three dilations. Features of perforation include dyspnea, malaise, tachycardia, fever, and subcutaneous crepitations. The majority are detected during the procedure or by the presence of pneumomediastinum, or pneumothorax or hydrothorax on chest radiograph, but occasionally contrast esophagography or esophagoscopy is required for confirmation. The death rate from perforation is 16% to 23% [79]. Early or prophylactic bougienage is of unclear benefit and has been associated with an increased risk of perforation. One study has shown a decrease in the number of dilatations required following interlesional steroid injection [80].

Placement of specialized nasogastric tubes or stents has lowered the rate of stricture formation in uncontrolled clinical trials and is superior to steroids in animal experiments [81]. An additional benefit of combining the use of a stent with systemic steroids has been suggested [81]. Oral sucralfate and H_2-blockers have no proven benefit in increasing tissue healing or reducing complications [82].

Surgery may ultimately be required if there is complete or near-complete obliteration of the esophageal lumen for more than 3 cm, if dysphagia recurs within a few weeks after successful dilation, or if perforation occurs during dilation [74]. Occasionally, resection and end-to-end anastomosis are possible, but usually extensive reconstruction, with colonic interposition, is necessary. The overall mortality from colonic replacement surgery is 2.0% to 3.6% and commonly results from sepsis secondary to anastomosis leakage or colonic graft necrosis [83]. Gastrectomy or gastrojejunostomy may also be required if gastric outlet obstruction develops [84]. Early definitive surgery for gastric outlet obstruction appears to be more advantageous than staged surgery [85]. Endoscopic balloon dilation may be an acceptable alternative procedure [86]. Diode laser-assisted radial lysis using a rigid endoscope has also been used to treat strictures successfully [87].

Supportive management is the mainstay of treatment for systemic toxicity. Heavy metal, cyanide, and hydrogen sulfide poisoning may require antidotal therapy (see Chapter 133). Neurologic toxicity due to hydrazine may respond to intravenous pyridoxine, administered at an initial dose of 25 mg per kg repeated in several hours, if necessary [42] (see Chapter 137). Methemoglobinemia may require treatment with methylene blue (see Chapter 117). Hemodialysis may enhance the elimination of heavy metals and dichromate, particularly if renal failure develops [88].

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CHAPTER 131 ■ SALICYLATE AND OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUG POISONING

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Nonsteroidal anti-inflammatory drugs (NSAIDs) include aspirin, related salicylates (Table 131.1), and a variety of other drugs (e.g., ibuprofen, indomethacin, phenylbutazone, and ketorolac), which modulate inflammation by inhibiting cyclooxygenase (COX). In clinical use for 100 years, aspirin still enjoys widespread popularity in the adult population, both by self-medication and by physician-recommended usage.

While the institution of child-resistant packaging and concerns about Reye's syndrome resulted in a dramatic decline in pediatric overdose, aspirin remains a leading cause of death due to pharmaceutical overdose [1–3]. Reducing the amount of aspirin available over the counter was associated with a fewer overdose deaths in the United Kingdom [4]. Nevertheless, vigilance remains necessary because chronic salicylate intoxication, particularly in the elderly, is commonly unrecognized or mistaken for other conditions, such as dehydration, dementia, sepsis, and multiorgan failure. In contrast, most other NSAIDs have a substantially greater safety margin than aspirin in overdose. Although availability without prescription has resulted in increased use and frequency of overdose, significant acute toxicity is uncommon [1,5,6].

PHARMACOLOGY

All NSAIDs have analgesic and antipyretic as well as anti-inflammatory activity. These effects are due to inhibition of COX, also known as *prostaglandin G/H synthase*, the enzyme responsible for the conversion of arachidonic acid to prostaglandins and thromboxanes [7,8]. The analgesic dose of most NSAIDs is approximately one-half the anti-inflammatory dose. For some NSAIDs, such as aspirin, ibuprofen, and fenoprofen, this gap is larger, whereas the converse is true for sulindac and piroxicam [9]. Antipyretic effects appear to be due to decreased pyrogen production peripherally as well as to a central hypothalamic effect. The existence of central nervous system (CNS) sites of action mediating analgesic activity has been postulated [10].

Two isoforms of COX have been characterized: COX-1, constitutionally present in platelets, endothelium, gastric mucosa, and the kidneys; and COX-2, induced by a variety of inflammatory mediators (e.g., cytokines, endotoxin, growth factors, hormones, and tumor promoters) but suppressed by glucocorticoids [8,11]. The anti-inflammatory and analgesic properties of NSAIDs appear to be primarily due to the inhibition of COX-2. Their adverse effects on gastric mucosa (e.g., hemorrhage, ulceration, and perforation) and kidney function (e.g., decreased renal blood flow and glomerular filtration rate), and their effects on platelet function appear to be mediated primarily by COX-1, but COX-2 inhibition may also be involved [8,12,13].

NSAIDs can be classified on the basis of their selectivity for COX-2. In particular, the coxibs rofecoxib, valdecoxib, and celecoxib were developed specifically for their COX-2 selectivity and the promise of improved safety. However, an increased risk of thrombotic events, primarily myocardial infarction and stroke, was identified in clinical trials and led to regulatory restrictions on the selective COX-2 inhibitors [14,15]. These adverse cardiovascular effects appear to be due to a relative excess of COX-1–generated thromboxane A2, which is vasoconstrictive and platelet-activating (i.e., prothrombic), and a relative lack of COX-2–generated prostaglandin I_2 (prostacyclin), which is vasodilatory and platelet inhibitory (i.e., antithrombotic) [8,14]. It is important to note that traditional NSAIDS diclofenac, meloxicam, and nabumetone exhibit partial COX-2 selectivity, and that other traditional, nonselective NSAIDs may also contribute to adverse cardiovascular events. Thus, selectivity is relative, and all NSAIDs inhibit both COX isoforms in a dose-dependent manner.

Inhibition of COX-1 may result in increased lipoxygenation of arachidonic acid to leukotrienes. This alternate metabolic pathway seems to be responsible for the sometimes fatal allergic reactions to NSAIDs especially prevalent in adults with asthma

TABLE 131.1

SALICYLATE PREPARATIONS

Compound	Common/trade names	Percentage salicylate
Acetylsalicylic acid	Aspirin	75
Bismuth subsalicylate	In Pepto-Bismol	37
Choline salicylate	Arthropan	56
Choline and magnesium salicylate	Trilisate	76
Difluorophenyl salicylic acid	—	—
Diflunisal	Dolobid	—[a]
Homomenthyl salicylate	In sunscreens	51
Magnesium salicylate	Doan's Caplets, Magan	90
Methyl salicylate	Oil of wintergreen	89
Salicylic acid	In topical keratolytics	100
Salicylsalicylic acid	Salsalate, Disalcid	96
Sodium salicylate	Pabalate	84
Trolamine salicylate	Aspercreme	48

[a]Not hydrolyzed to salicylic acid but may cause screening tests for salicylate to be falsely positive.

and nasal polyps [16,17]. The expression or upregulation of COX-2 may be involved in the pathogenesis of Alzheimer's disease and some cancers (e.g., colon).

Aspirin (acetylsalicylic acid) is unique in that it acetylates a serine residue near the active site of COX, thereby irreversibly inhibiting its catalytic function. In contrast, the inhibition of COX by other NSAIDs is reversible and transient. This difference in activity is most notable in platelets, in which thromboxane A_2 is essential for normal function [18]. Even in low doses (80 mg), aspirin inhibits platelet aggregation and prolongs the bleeding time for up to 1 week (pending the production of new platelets), whereas other NSAIDs do not have clinically significant platelet effects [19].

In high doses, aspirin and other salicylates also inhibit the hepatic synthesis of clotting factor VII and, to some degree, factors IX and X, thereby prolonging the prothrombin time. This effect appears to be due to interference with the activity of vitamin K and can be reversed by administration of phytonadione (vitamin K_1). In contrast, other NSAIDs have insignificant effects on clotting-factor synthesis [19].

Salicylates

Salicylates are available in oral, rectal, and topical formulations. Enteric-coated and sustained-release aspirin tablets are also marketed. Aspirin preparations frequently contain other drugs such as anticholinergics, antihistamines, barbiturates, caffeine, decongestants, muscle relaxants, and opioids. The recommended pediatric dose of aspirin is 10 to 20 mg per kg of body weight every 6 hours, up to 60 mg per kg per day; for adults, the recommended dose is 1,000 mg initially, followed by 650 mg every 4 hours for anti-inflammatory effect. Therapeutic doses of other salicylate salts are similar but depend on their salicylate content (see Table 131.1) and formulation. After a single oral dose of aspirin, therapeutic effects begin within 30 minutes, peak in 1 to 2 hours, and last approximately 4 hours.

Being a weak acid (pK_a, 3.5), aspirin is predominantly nonionized at gastric pH and, therefore, theoretically well absorbed in the stomach. However, gastric acidity reduces the solubility of aspirin, thereby slowing the dissolution of tablets. Hence, despite its higher pH, most absorption actually occurs in the small intestine, probably because of its much larger surface area. Peak serum salicylate levels of 10 to 20 mg per dL (0.7 to 1.4 mmol per L) occur 1 to 2 hours after ingestion of a single therapeutic dose. Levels up to 30 mg per dL can occur with long-term therapy and may be necessary for maximal anti-inflammatory effects in some patients. Absorption is delayed or prolonged after ingestion of enteric-coated or sustained-release preparations and suppository use [20]. With overdose, slow pill dissolution, and delayed gastric emptying due to aspirin-induced pylorospasm may lead to absorption continuing for 24 hours or longer after ingestion [21].

During absorption, aspirin is rapidly hydrolyzed by plasma esterases to its active metabolite, salicylic acid. At physiologic pH, salicylic acid (pK_a: 3.0) is more than 99.9% ionized to salicylate, which, in contrast to nonionized salicylic acid, diffuses poorly across cell membranes. The drug may become sequestered preferentially in inflamed tissue due to this pH-dependent ionization.

The apparent volume of distribution of salicylate at pH 7.4 is only 0.15 L per kg, in part due to its extensive protein binding. Only free (i.e., unbound) salicylate is pharmacologically active. However, salicylate is unique in that its apparent volume of distribution is not constant. High drug levels (e.g., as a result of chronic therapeutic dosing or acute overdose), low albumin levels, and the presence of other drugs that bind to albumin increase the amount and fraction of free drug [22]. When this occurs, the apparent volume of distribution may increase to 0.60 L per kg [23]. Acidemia, as a consequence of either concomitant illness or severe poisoning, may additionally increase the fraction of nonionized, diffusible drug, promote its tissue penetration, and increase the apparent volume of distribution even more.

After single therapeutic doses, salicylate is metabolized in the liver to the inactive metabolites salicyluric acid (the glycine conjugate; 75% of the dose), salicyl phenolic glucuronide (10%), salicyl acyl glucuronide (5%), and gentisic acid (less than 1%). The remaining 10% of the dose is excreted unchanged in the urine. When serum concentrations exceed 20 mg per dL, the two main pathways of metabolism become saturated, and elimination changes from first order (i.e., proportional to the serum level) to zero order (constant), as described by Michaelis–Menton kinetics. Hence, the apparent half-life of salicylate is 2 to 3 hours after a single therapeutic dose, 6 to 12 hours with chronic therapeutic dosing (i.e., serum levels of 20 to 30 mg per dL), and 20 to 40 hours with overdose (i.e., when levels exceed 30 mg per dL) [24]. Because of saturable metabolism, a small increase in the daily dose can lead to a large increase in serum drug levels, with the potential

for unintentional poisoning [25]. Depletion of glycine stores may reduce the capacity of the salicyluric acid pathway and further slow elimination in overdose [26].

Renal excretion of salicylate becomes the most important route of elimination when hepatic transformation becomes saturated. The rate of excretion is determined by the glomerular filtration, active proximal tubular secretion of salicylate, and passive distal tubular reabsorption of salicylic acid. Alkalinization of the urine decreases the passive reabsorption of salicylic acid by converting it to ionized, nondiffusible salicylate and thereby increases drug excretion. Similarly, increasing the rate of urine flow increases drug clearance by increasing the glomerular filtration and decreasing the distal tubular reabsorption of salicylic acid (by diluting its concentration in the tubular lumen). Combined alkalinization and diuresis can augment the renal elimination of salicylate by 20-fold or more [27,28]. Conversely, dehydration and aciduria perhaps due to preexisting illness or to salicylate poisoning itself decrease salicylate excretion, and increase the duration of toxicity once it develops.

Salicylates readily cross the placenta and enter breast milk. Salicylate elimination in the fetus or infant may be prolonged because of immature metabolic pathways and renal function [29]. It may also be prolonged in patients with liver or renal disease.

The pathophysiology of salicylate poisoning is multifactorial [30–35]. Initially and in mild poisoning, direct stimulation of the respiratory center in the medulla by toxic salicylate concentrations results in a respiratory alkalosis, unless blunted by concomitant ingestion of CNS depressants [31]. Direct stimulation of the medullary chemoreceptor zone and irritant effects on the gastrointestinal tract are responsible for nausea and vomiting. Exaggerated antipyretic effects involving the hypothalamus may cause vasodilation and sweating [36]. Dehydration results from gastrointestinal, skin, and insensible fluid losses. The osmotic diuresis that occurs as bicarbonate is excreted in response to alkalemia also contributes to dehydration. Sodium and potassium depletion result from excretion of these electrolytes along with bicarbonate (in exchange for hydrogen ion reabsorption). A functional hypocalcemia (decreased ionized calcium) may accompany alkalemia and cause or contribute to cardiac arrhythmias, tetany, and seizures.

Subsequently, in moderate poisoning, the accumulation of salicylate in cells causes uncoupling of mitochondrial oxidative phosphorylation, inhibition of the Krebs cycle, inhibition of amino acid metabolism, and stimulation of gluconeogenesis, glycolysis, and lipid metabolism [37,38]. These derangements result in increased but ineffective metabolism, with increased glucose, lipid, and oxygen consumption and increased amino acid, carbon dioxide, glucose, ketoacid, lactic acid, and pyruvic acid production. High serum levels of organic acids contribute to an increased anion-gap metabolic acidosis, and the renal excretion of these acids results in aciduria. However, increased carbon dioxide production further stimulates the respiratory center, and the respiratory alkalosis persists, resulting in alkalemia with paradoxical aciduria. An osmotic diuresis further accentuates fluid and electrolyte losses.

In severe poisoning, progressive dehydration and impaired cellular metabolism cause multisystem organ dysfunction. Metabolic acidosis with acidemia becomes the dominant acid–base disturbance. Respiratory acidosis, lactic acidosis, and impaired renal excretion of organic acids due to dehydration and acute tubular necrosis contribute to the acidemia. Acidemia increases the fraction of nonionized salicylate in serum, thereby promoting its tissue penetration and toxicity, and rapid clinical deterioration may ensue with increasing brain salicylate levels. Impaired cellular metabolism can cause increased capillary permeability [39] leading to cerebral edema and noncardiogenic pulmonary edema or acute respiratory distress syndrome. Coma and seizures may result from impaired cellular metabolism, cardiovascular depression, cerebral edema, acidemia, hypoglycemia, and acute white matter damage due to myelin disintegration and activation of glial caspase-3 [41,42]. Respiratory alkalosis may be replaced by respiratory acidosis if coma or seizures cause respiratory depression. Tissue hypoxia resulting from pulmonary edema, impaired perfusion, or seizures may lead to anaerobic metabolism and concomitant lactic acidosis.

Hemorrhagic diathesis may result from increased capillary fragility, decreased platelet adhesiveness, thrombocytopenia, and coagulopathy secondary to liver dysfunction. It occurs primarily in patients with chronic poisoning.

Other Nonsteroidal Anti-inflammatory Drugs

Despite their structural diversity, the pharmacokinetics of traditional NSAIDs are quite similar. Like aspirin, they are weak acids, with pK_a ranging from 3.5 to 5.6 and pH-dependent ionization being the major determinant of tissue distribution and sequestration. They are rapidly absorbed after ingestion, have small volumes of distribution (0.08 to 0.20 L per kg), and are 90% to 99% protein bound (principally to albumin). Most have half-lives of less than 8 hours, with low non–flow-dependent hepatic clearance, primarily by the CYP2C subfamily of cytochrome P450 enzymes, to inactive metabolites that are then conjugated, mostly with glucuronic acid, and excreted in the urine. Sulindac is one exception in that its sulfide metabolite is the active form of the drug and has a half-life of 16 hours [42]. Nabumetone is also a prodrug, and its active metabolite, 6-methoxy-2-naphthylacetic acid, has a half-life of more than 20 hours (and even longer in the elderly) [43]. Phenylbutazone, oxyphenbutazone, and piroxicam are notable for half-lives of longer than 30 hours. Diflunisal, like aspirin, has a dose-dependent half-life of 5 to 20 hours. Indomethacin, sulindac, etodolac, piroxicam, carprofen, and meloxicam undergo enterohepatic recirculation [42,44,45]. Small amounts (less than 10%) of nonsalicylate NSAIDs are excreted unchanged in the urine, limiting the effect of urine pH on clearance. The coxibs are nonacidic drugs [13], highly protein bound and primarily metabolized in the liver.

In contrast to salicylates, the metabolism of most nonsalicylate NSAIDs is not saturable or prolonged in overdose, and elimination follows first-order kinetics. An exception is phenylbutazone, whose elimination may follow Michaelis–Menton kinetics.

Toxic effects of NSAIDs appear to be primarily due to exaggerated pharmacologic effects, with gastric irritation and renal dysfunction resulting from the inhibition of prostaglandin synthesis [46]. In contrast to salicylate poisoning, the acidosis that sometimes occurs with large overdoses of these agents appears to be due to high levels of parent drug and metabolites rather than to disruption of metabolism [47]. Mechanisms responsible for their CNS toxicity remain to be defined.

CLINICAL TOXICITY

Salicylates

Salicylate poisoning may occur with acute as well as chronic overdose [30–35,48–55]. It most commonly results from ingestion, but poisoning due to topical use [56] and rectal self-administration [57] has been reported. The ingestion of topical preparations of methyl salicylate (oil of wintergreen, also present in Chinese propriety medicines) can result in

TABLE 131.2

SEVERITY OF SALICYLATE POISONING

Severity grade	Serum pH	Underlying acid–base abnormality
Mild	> 7.45	Respiratory alkalosis
Moderate	7.35–7.45	Combined respiratory alkalosis and metabolic acidosis
Severe	< 7.35	Metabolic acidosis with or without respiratory acidosis

rapid-onset poisoning, due to its concentration, rapid absorption kinetics, and higher lipid solubility [58]. Infants may become poisoned by ingesting the breast milk of women chronically taking therapeutic doses of salicylate [59]. Intrauterine fetal demise resulting from poisoning during pregnancy [60] and neonatal poisoning resulting from the transplacental diffusion of therapeutic doses of salicylate taken before delivery [61] have also been described. Delays to presentation, diagnosis, and chronicity each increase the severity and mortality [50,62,63] and with severe poisoning, the fatality rate may be as high as 50% [51,55].

Regardless of whether poisoning is acute or chronic, it can be characterized as mild, moderate, or severe on the basis of the serum pH and underlying acid–base disturbance (Table 131.2). This approach was first described in the classic papers by Done [48,64], who also developed a nomogram that attempted to correlate the severity of poisoning with a timed salicylate level after acute ingestion. Although Done's nomogram has subsequently been shown to have poor predictive value in acute poisoning [49] and is not applicable to chronic poisoning, to acute poisoning by enteric-coated aspirin and nonaspirin salicylates, or to patients with acidemia [62] his observation that the clinical severity of poisoning correlates with acid–base status remains undisputed.

Mild poisoning is characterized by alkalemia (serum pH greater than 7.45) and a pure respiratory alkalosis. It may develop 2 to 8 hours after acute ingestion of 150 to 300 mg per kg of aspirin [48,64] or any time during chronic therapy. Associated signs and symptoms include nausea, vomiting, abdominal pain, headache, tinnitus, tachypnea (or subtle hyperpnea), ataxia, dizziness, agitation, and lethargy. The anion gap (see Chapter 71) is normal until late in this stage, when compensatory renal bicarbonate excretion eventually lowers the serum bicarbonate level. Serum glucose, potassium, and sodium values may be high, low, or normal. Despite total body fluid and electrolyte depletion and clinical dehydration, laboratory evidence of dehydration (e.g., hemoconcentration, increased serum blood urea nitrogen [BUN] and creatinine, increased urine specific gravity) may be absent.

Moderate poisoning is characterized by a near normal serum pH (7.35 to 7.45) with an underlying metabolic acidosis as well as respiratory alkalosis. It can occur 4 to 12 hours after an acute overdose of 300 to 500 mg per kg of aspirin [48,64]. It may also occur in patients with chronic ingestion who delay seeking medical care for symptoms of mild poisoning and continue to take salicylate. Electrolyte analysis demonstrates a low serum bicarbonate value with an increased anion gap. Gastrointestinal and neurologic symptoms are more pronounced. There may be agitation, fever, asterixis, diaphoresis, deafness, pallor, confusion, slurred speech, disorientation, hallucinations, tachycardia, tachypnea, and orthostatic hypotension. Coma and seizures can also occur. Leukocytosis, thrombocytopenia, increased or decreased serum glucose and sodium values, hypokalemia, and increased serum BUN, creatinine, and ketones may be present.

Severe poisoning is defined by the presence of acidemia (serum pH less than 7.35) with underlying metabolic acidosis and respiratory alkalosis or acidosis and a high anion gap. It can occur 6 to 24 hours or more after the acute ingestion of more than 500 mg per kg of aspirin [48,64] or in unrecognized or untreated chronic poisoning. Severe dehydration and marked sinus tachycardia are often present. Other findings may include coma, seizures, papilledema, hypotension, dysrhythmias, congestive heart failure, oliguria, hypothermia or hyperthermia, rhabdomyolysis and multiple organ failure [55,63,65,66]. Laboratory abnormalities are similar to those seen in moderate poisoning but are more pronounced. Hypoglycemia, pulmonary edema and cerebral edema or hemorrhage may be present [54,67]. Asystole is the most common terminal dysrhythmia, but ventricular tachycardia and ventricular fibrillation can also occur [54,55,68,69]. When cardiac arrest occurs, death appears to be inevitable. Successful resuscitation in this situation has yet to be reported [69].

Although an increased anion-gap metabolic acidosis is often said to be a hallmark of salicylate poisoning, in reality a variety of acid-base disturbances may be seen depending on the delay to presentation and severity of poisoning. As noted earlier, the anion gap may be normal and acidosis absent in early or mild intoxication. In addition, the anion gap is rarely above 20 mEq per L, even in advanced poisoning [31]. It is, therefore, more appropriate to say that an abnormal acid–base status is the hallmark of salicylate poisoning. In adults, combined respiratory alkalosis and metabolic acidosis is the most common finding (50% to 61%), followed by pure respiratory alkalosis (20% to 25%), pure metabolic acidosis (15% to 20%), and a combined respiratory and metabolic acidosis (5%) [31,55]. Metabolic acidosis is more common and respiratory alkalosis less common (and often absent) in children than in adults [50,55] suggesting that children progress more rapidly from mild-to-moderate to severe poisoning, perhaps because of more rapid and extensive tissue distribution of drug [70]. Metabolic acidosis is also more common in patients with large acute ingestions, chronic intoxication, and delayed presentation or treatment [31,50,51,55,71]. The onset and progression of toxicity may be delayed after overdose with enteric-coated or sustained-release formulations [20].

Potential complications of both therapeutic and toxic doses of salicylate include gastrointestinal tract bleeding, increased prothrombin time, hepatic toxicity, pancreatitis, proteinuria, and abnormal urinary sediment. Significant bleeding, gastrointestinal tract perforation, blindness, and inappropriate secretion of antidiuretic hormone are rare complications of acute poisoning.

Other Nonsteroidal Anti-inflammatory Drugs

With the exception of mefenamic acid and phenylbutazone, significant toxicity from acute overdose is unusual. Manifestations typically include nausea, vomiting, abdominal pain, headache, confusion, tinnitus, drowsiness, and hyperventilation [5,72,73]. Glycosuria, hematuria, and proteinuria are also common. Occasionally, acute renal failure (acute tubular necrosis or interstitial nephritis) can develop. Symptoms rarely last more than several hours, and acute renal toxicity is almost always reversible over a period of a few days to a few weeks. Experience with selective COX-2 inhibitor overdose is limited, but acute toxicity appears to be similar [74].

Muscle twitching and grand mal seizures have been reported in 30% of mefenamic acid overdoses [75]. Apnea, coma, and cardiac arrest can also occur [75]. Metabolic acidosis, coma, seizures, hepatic dysfunction, hypotension, and cardiovascular

collapse are relatively frequent after phenylbutazone overdose [72,73,76–78]. Uncommonly, coma, hyperactivity, hypothermia, seizures, metabolic acidosis, acute renal insufficiency, thrombocytopenia, acute respiratory distress syndrome, upper gastrointestinal tract bleeding, and respiratory depression are seen in ibuprofen poisoning [47,78–87]. Death can result from ibuprofen alone or combined with other drugs [1,88–90], but despite the frequency of overdose, it is extremely rare [1,5,6]. Seizures and metabolic acidosis have also been reported in ketoprofen and naproxen poisoning [91,92].

Minimum toxic and lethal doses are not well defined. Little correlation was found between the amount of ibuprofen reportedly ingested and symptoms in adults [77]. In the pediatric population, however, the mean amount ingested was much greater in symptomatic patients (440 mg per kg) than asymptomatic ones (114 mg per kg) [79]. The spectrum of toxicity appears to be the same in children and adults [90]. Elderly patients are at increased risk of developing toxicity with both therapeutic doses and overdoses [93]. Even with severe poisoning, complete recovery usually occurs within 24 to 48 hours.

DIAGNOSTIC EVALUATION

The history should include the time or times of ingestion, the specific product and formulation, the amount ingested, and any concomitant ingestion or medication use. Physical examination should focus on vital signs, neurologic and cardiopulmonary function, and assessment of the state of hydration. Vital signs should include an accurate temperature and respiratory rate and, if possible, orthostatic measurements of pulse and blood pressure. The fundi should be examined for papilledema. Stool and urine should be tested for occult blood. Peritoneal signs should be sought on abdominal examination.

Salicylates

Laboratory evaluation of patients with salicylate poisoning should include arterial or venous blood gases, complete blood cell count, serum electrolyte, glucose, BUN, creatinine, and salicylate levels, and urinalysis. Patients with moderate-to-severe salicylate poisoning should also have serum calcium, magnesium, and ketones, liver function tests, coagulation profile, electrocardiogram; and chest radiograph. Because patients often confuse aspirin and acetaminophen, testing should be performed for both.

The ferric chloride spot test can be used to rapidly detect the presence of salicylate in urine or commercial products [94]. Several drops of 10% ferric chloride added to urine turn purple if salicylate is present. A positive urine test indicates exposure but not overdose because positive results are seen with therapeutic dosing. False-positive reactions may be caused by acetoacetic acid, phenylpyruvic acid, phenothiazines, and phenylbutazone. A quantitative serum salicylate level is necessary to confirm the diagnosis of poisoning. Diflunisal may result in falsely elevated salicylate levels when measured by fluorescence polarization immunoassay or the Trinder colorimetric assay [95].

Salicylate levels must be interpreted with respect to the duration (i.e., acute vs. chronic overdose) and time of ingestion. At similar salicylate levels, patients with chronic poisoning tend to be more ill than those with acute poisoning [32,54,55]. Soon after an acute overdose, levels can be quite high (e.g., greater than 60 mg per dL) in the absence of significant toxicity. Conversely, with chronic overdosage and late in the course of an acute overdose, moderate or severe toxicity may be present despite serum salicylate concentrations in the high therapeutic range. At similar salicylate levels, children, the elderly, and those with underlying disease tend to be more ill than otherwise healthy adults [32,52,70,96]. Poisoning in such patients, particularly if chronic, can occasionally be seen with therapeutic salicylate levels. Hence, as noted previously, the severity of poisoning is ultimately determined by acid–base status and clinical findings.

Serial salicylate levels are necessary for confirming the efficacy of gastrointestinal tract decontamination and enhanced elimination procedures but do not obviate the need for continued clinical and metabolic monitoring. Depending on the severity and course of poisoning, drug levels and other laboratory tests should be repeated at 2- to 6-hour intervals. Monitoring of drug levels for at least 12 hours is necessary to exclude significant ongoing absorption after overdose.

Historically, at least 25% of patients with chronic salicylate poisoning are initially undiagnosed [31,51,71]. These patients are typically elderly, have a variety of presenting complaints and underlying illnesses, and have been medicating themselves with aspirin. To avoid missing the diagnosis, all patients should be asked specifically about the use of nonprescription drugs. Asking about tinnitus or hearing distortion, which occurs with salicylate levels in the high end of the therapeutic range (i.e., 20 to 30 mg per dL), may also suggest the diagnosis in patients with unknown ingestions or unexplained complaints. Occult salicylate poisoning should be considered in any patient with an unexplained acid–base disturbance, altered mental status, fever, diaphoresis, dyspnea, vomiting, and pulmonary edema [31,71].

The differential diagnosis of salicylate poisoning includes infection (particularly meningitis); CNS trauma and tumors; congestive heart failure; chronic obstructive pulmonary disease; carbon monoxide, isoniazid, lithium, and valproate intoxication; toxic gas inhalation; and other toxic causes of an elevated anion-gap acidosis, particularly methanol and ethylene glycol (see Chapters 71 and 119). Hemodynamic, autonomic, and laboratory manifestations of severe poisoning resemble the systemic inflammatory response syndrome and may be mistaken for sepsis [61,65,66,97]. Salicylate poisoning has also been misdiagnosed as alcohol intoxication, alcohol withdrawal, dementia, diabetic ketoacidosis, impending myocardial infarction, nonspecific asterixis and encephalopathy, and viral encephalitis.

In infants and children, salicylate poisoning may be confused with inborn errors of metabolism. It may be particularly difficult to distinguish from Reye's syndrome, because they are not only similar in presentation but appear to be interrelated [98,99]. Fatty infiltration of the liver on pathologic examination of a biopsy specimen, low (i.e., subtherapeutic) cerebrospinal fluid salicylate levels, and high alanine, glutamine, and lysine levels indicate Reye's syndrome rather than salicylate poisoning. Radiopaque densities in the stomach on abdominal radiograph suggest the possibility of an enteric-coated or sustained-release formulation or a magnesium or bismuth salt of salicylate [100].

Other Nonsteroidal Anti-inflammatory Drugs

The initial evaluation of patients with nonsalicylate-NSAID overdose is similar to that for salicylates. Evaluation of acid–base, electrolyte, and renal parameters is particularly important. Additional ancillary testing is dictated by clinical severity. Quantitative serum levels of nonsalicylate NSAIDs are neither routinely available nor necessary for treatment.

Many medical conditions and other intoxications cause signs and symptoms similar to those seen in nonsalicylate NSAID poisoning. In the absence of a history of ingestion, the diagnosis is made by exclusion of other etiologies.

MANAGEMENT

Salicylates

Supportive care, limiting drug absorption, and enhancing drug elimination are the goals of therapy. Resuscitative measures should be instituted as necessary. It is critically important to remember that, should endotracheal intubation be necessary, hyperventilation must be accomplished before, during, and after this procedure to prevent worsening acidemia, which increases the fraction of nonionized salicylic acid available for tissue distribution, thereby enhancing toxicity. The administration of respiratory depressants or failure to adequately hyperventilate unconscious or paralyzed patients can result in rapid deterioration and death of severely poisoned patients [62,68,101]. Because an increase in the partial pressure of carbon dioxide (PCO_2) is almost inevitable following intubation and mechanical ventilation, it is recommended that patients with arterial PCO_2 values below 20 mm Hg be given an intravenous bolus of 1 to 2 mEq per kg sodium bicarbonate at the time of intubation. Arterial blood gases should always be checked after intubation and after bicarbonate therapy.

Because CNS hypoglycemia may occur despite a normal serum glucose value [101], 50 mL of 50% dextrose in water should be given intravenously to any patient with an altered mental status whose capillary glucose concentration is not already elevated [49]. Anticonvulsants (e.g., benzodiazepines, propofol, and barbiturates) as well as supplemental glucose should be given to patients with seizures. It is also prudent to treat seizures with $NaHCO_3$, as acidemia is likely to worsen. Hyperthermia should be treated with cooling blankets, ice packs, and evaporative methods (see Chapter 66).

Central venous pressure monitoring may be necessary for optimal treatment of hypotension, especially if there is evidence of heart failure or pulmonary edema. Patients with noncardiac pulmonary edema should be treated with positive pressure ventilation rather than diuretics. Again, maintaining hyperventilation and reducing acidemia are critical in patients with compromised pulmonary function.

Additional supportive measures are directed at correction of dehydration and metabolic derangements. The degree of dehydration parallels the severity of poisoning [64], but it is often unappreciated, underestimated, or undertreated. Patients with mild, moderate, or severe poisoning typically have volume deficits of 1 to 2, 3 to 4, or 5 to 6 L (20, 40, and 60 mL per kg in children), respectively. In the presence of acidemia, hypokalemia is more severe than indicated by the serum potassium level (by approximately 0.6 mEq per L for each 0.1 unit of decrease in pH) and should be treated aggressively.

Acidemia should also be treated aggressively with intravenous $NaHCO_3$. Since the respiratory alkalosis is a concomitant primary acid–base disturbance and not just a compensatory response, the administration of bicarbonate is unlikely to blunt the respiratory drive and increase the PCO_2, which might otherwise limit the change in serum pH. In addition, the goal of therapy is to limit the tissue distribution of salicylates by increasing the serum pH. The dose of bicarbonate needed may be substantial, and is typically 4 to 5 ampules or 200 to 300 mEq in an adult with severe poisoning.

As with repleting volume, at least half of the $NaHCO_3$ deficit should be given during the first hour either by continuous infusion or by 0.5 to 1.0 mEq per kg boluses every 10 minutes. Arterial blood gases should be reevaluated during after such therapy. Potential complications of $NaHCO_3$ administration include excessive alkalemia, hypokalemia, hypocalcemia, hypernatremia, and fluid overload. Relative contraindications to hypertonic $NaHCO_3$ include oliguric renal failure, congestive heart failure, and cerebral or pulmonary edema.

Tetany should be treated with intravenous calcium chloride or calcium gluconate (10 mL of a 10% solution over 5 to 10 minutes). Fresh-frozen plasma, red blood cell, and platelet transfusions may be required for patients with active bleeding or significant blood loss. Asymptomatic increases in international normalized ratio can be treated with subcutaneous vitamin K.

Gastrointestinal decontamination should be performed in all patients with intentional overdoses and those with accidental ingestions of greater than 150 mg per kg. Because of delayed absorption, decontamination may be effective for as long as 24 hours after overdose, even in patients with spontaneous vomiting [21]. Considerable diversity in opinion exists, however, regarding the optimal method of decontamination [103].

Activated charcoal is effective in preventing salicylate absorption in simulated overdose [104] and, therefore, it is recommended for all significant ingestions, regardless of delay in presentation. Multiple oral doses of charcoal [105] or gastric lavage preceded and followed by another dose of activated charcoal may be the more effective for preventing the absorption of large overdoses [106]. Many grams of aspirin have been recovered by lavage up 24 hours after ingestion [21]. Repeated doses of activated charcoal or whole-bowel irrigation may be effective for patients who have ingested enteric-coated or sustained-release formulations and those with serum drug levels that continue to rise despite other decontamination measures [107].

The efficacy of multiple-dose charcoal therapy in enhancing salicylate elimination may depend on the formulation. Increases in serum salicylate elimination reported using an effervescent preparation containing bicarbonate [108] could not be replicated with multiple doses of noneffervescent charcoal in simulated overdose (i.e., less than 3 g) in humans [109–112]. Oral charcoal does not substantially accelerate the elimination of intravenously administered salicylic acid in pigs, discounting the role of gut dialysis or enterohepatic circulation [113]. If multiple-dose charcoal is used, sorbitol should not be included with the subsequent doses [114,115].

Salicylate elimination can be enhanced by urine alkalinization and diuresis [27,28,32–34,116], extracorporeal removal [117], and perhaps by glycine administration [52]. It should be emphasized that serum and urine alkalinization and establishing a urine output of 1 to 2 mL per kg per hour are equally important goals in the management of patients with salicylate toxicity [35,118,119]. Moreover, alkalinization of the urine is difficult to achieve in patients with acidemia and aciduria (i.e., severe clinical toxicity) [64]. Theoretical concerns regarding pulmonary or cerebral edema should not preclude aggressive fluid therapy, as administering only maintenance fluids intravenously is insufficient treatment for a patient with salicylate poisoning.

Indications for urine alkalinization and alkaline diuresis include acid-base abnormalities and systemic symptoms with a salicylate level that is greater than 30 mg per dL after an acute overdose. Patients with chronic overdoses may be symptomatic and require treatment, despite lower salicylate levels. The goal is to achieve a urine pH of 7.5 or greater. All patients treated with alkaline diuresis need close monitoring in an intensive care unit or similar setting. Bladder catheterization is essential in those with moderate or severe poisoning, in whom hourly monitoring of urine output and pH is required. Arterial or venous blood gases, electrolytes, BUN, creatinine, glucose, and salicylate concentrations should initially be rechecked at 2- to 4-hour intervals, depending on the severity of poisoning, the results of previous testing, and the response to therapy. Cardiac monitoring and frequent reevaluations of vital signs, mental status, and pulmonary function are also necessary during alkaline diuresis.

Alkalinization of the urine may be impossible to achieve in the presence of dehydration and hypokalemia because hydrogen ions are excreted in exchange for reabsorbed sodium and potassium, respectively [62,120]. Therefore, correction of fluid and potassium deficits is critical.

The amount of bicarbonate and supplementary potassium necessary to achieve and maintain an alkaline urine depends on the severity of poisoning (Table 131.2). For example, the initial intravenous fluids for a moderately poisoned patient could be 1 L of 5% dextrose in one-half normal saline to which 75 mEq of sodium bicarbonate (i.e., 1.5 ampules of 8.4% sodium bicarbonate) and 40 mEq of potassium chloride have been added. In severe poisoning, however, 150 mEq of sodium bicarbonate (i.e., 3 ampules of 8.4% sodium bicarbonate) and 60 mEq of potassium chloride should be added to each liter of 5% dextrose in water initially, and adjusted as necessary. In patients with hypernatremia, a more hypotonic solution should be used. Again, the use of a dextrose-containing solution is important because of the potential for occult CNS hypoglycemia. Although forced diuresis (e.g., 500 mL per hour urine output in adults) is no longer recommended [121], a moderate rate of fluid administration (3 to 4 mL per kg per hour) is recommended. Although counterintuitive, even patients with mild poisoning (i.e., alkalemia) should be given bicarbonate (and fluids); this is necessary to replace ongoing renal losses and prevent deterioration. The onset of diuresis may be delayed an hour or two after the institution of therapy.

Carbonic anhydrase inhibitors (e.g., acetazolamide) should never be used to alkalinize the urine (especially without concomitant bicarbonate therapy) because the resultant systemic acidosis may promote tissue distribution of salicylate and result in clinical deterioration [122,123]. Similarly, the use of tris-hydroxymethyl aminomethane, an organic H^+ buffer that increases serum and urine pH, is not recommended. Although tris-hydroxymethyl aminomethane has been suggested for the treatment of acidemia and aciduria refractory to bicarbonate administration, it has not been studied in human salicylate poisoning and has a number of potential adverse effects (e.g., hypoglycemia, extravasation necrosis, phlebitis, respiratory depression, and increased intracellular pH leading to decreased pH gradients with increased tissue distribution and intracellular trapping of salicylate) [124].

As with $NaHCO_3$ therapy for acidemia, complications of alkaline diuresis include excessive alkalemia, hypokalemia, hypocalcemia, hypernatremia, and fluid overload [52,119,121]. Young children, the elderly, and those with severe poisoning are most susceptible to such complications. Alkaline diuresis is contraindicated in patients with oliguric renal failure, congestive heart failure, and cerebral or pulmonary edema. Such therapy should be withheld or discontinued if the serum pH exceeds 7.55.

Hemodialysis is indicated in patients with severe poisoning and those with moderate poisoning who fail to improve with alkaline diuresis [34–36,51,52,62]. Hemodialysis is essential for successful outcome in patients with coma, seizures, cerebral or pulmonary edema, and renal failure [36,55]. Whether the term *coma*, as used here, should include altered mental status (e.g., confusion and disorientation) and any impairment in the level of consciousness as well as unresponsiveness is controversial. Erring on the side of treatment is recommended. Acidemia and temperature greater than 38°C are associated with high mortality [55] and should also be considered potential indications for hemodialysis, particularly if the patient is resistant to bicarbonate and fluid therapy. Similarly, patients with moderate poisoning who have liver dysfunction and, hence, impaired ability to eliminate salicylate may also benefit from hemodialysis.

A high salicylate level is often cited as an indication for hemodialysis but recommendations vary widely with cutoffs ranging from 40 to 200 mg per dL (100 mg per dL being the most common) for acute ingestions and 60 to 80 mg per dL for chronic exposures [124]. In one study [51], salicylate levels in fatal cases ranged from 34 to 193 mg per dL and in another [54], some patients died with drug levels in the therapeutic range. Moreover, drug levels do not discriminate patients who die from survivors [54,55]. Clearly, the salicylate level should not be used as the sole indication for hemodialysis. Instead, the severity of poisoning is determined by clinical findings, which reflect tissue drug concentration and effect, depend on factors that influence tissue distribution, and do not necessarily correlate with blood levels, particularly when acidemia is present [122]. Moreover, a serum salicylate concentration should be interpreted in the context of a simultaneous measurement of serum pH. Hence, hemodialysis is appropriate for patients with high drug levels who have severe clinical toxicity (particularly acidemia), but it may not be necessary in those without such manifestations [55]. Conversely, patients with low salicylate levels, particularly those with significant underlying cardiorespiratory disease, should be treated with hemodialysis if they exhibit clinical or laboratory manifestations of severe toxicity. Because of delays inherent in the turnaround time for salicylate determinations and in preparing for hemodialysis, the projected clinical course should also be considered. Waiting for the salicylate level to reach some predetermined level before initiating hemodialysis in patients who are severely poisoned or deteriorating despite other treatments is ill-advised.

Hemodialysis is preferred over continuous renal replacement therapy or hemoperfusion due to the rapid clearances and correction of fluid, electrolyte and acid–base abnormalities achieved [117,126,127]. A high-bicarbonate (e.g., up to 40 mEq per L) dialysate solution (bath) should be used, and potassium should usually be added to the dialysate solution. Peritoneal dialysis and exchange transfusion are also less effective [128].

Failure to adequately correct fluid deficits prior to initiating hemodialysis can result in disastrous consequences. In contrast to the typical dialysis (i.e., renal failure) patient who is fluid overloaded, those with salicylate poisoning are typically hypovolemic. Uncorrected or occult hypovolemia can result in cardiovascular decompensation with hemodynamic instability and even cardiac arrest when dialysis is started because of the acute decrease in intravascular volume that occurs when blood is removed and used to prime the dialysis tubing and pump at the beginning of dialysis. This complication can be prevented or minimized by ensuring adequate volume resuscitation, giving a bolus of saline, and priming the tubing and pump with saline (rather than blood) prior to initiating dialysis.

Oral administration of glycine or *N*-glycylglycine has been used in overdose patients to promote drug clearance [26,129]. Because the conjugation of salicylic acid with glycine to form salicyluric acid becomes saturated and glycine levels decrease in overdose patients, supplemental glycine can enhance the formation and excretion of this metabolite. To date, clinical experience with this therapy is limited, its comparative efficacy is unknown, and the side effects of nausea and vomiting with glycine have been problematic. Doses used ranged from 8 g dissolved in water initially, followed by 4 g every 4 hours for 16 hours, to 20 g followed by 10 g every 2 hours for 10 hours for glycine. The dose for *N*-glycylglycine was 8 g dissolved in water followed by 2 to 4 g every 2 hours for 16 hours.

Other Nonsteroidal Anti-inflammatory Drugs

The treatment of nonsalicylate NSAID poisoning is supportive and symptomatic. Although most patients require only observation, airway protection, mechanical ventilation, and fluid resuscitation, use of anticonvulsants for seizures, bicarbonate

for acidosis, vitamin K or fresh-frozen plasma for coagulopathy, antacids and histamine$_2$–receptor antagonists for gastritis, and blood products for gastrointestinal tract bleeding may occasionally be required. Naloxone has been reported to reverse CNS depression in a toddler with ibuprofen toxicity [81]. Renal function should be monitored carefully in patients with abnormal urinalysis, underlying renal disease, or advanced age. Liver function tests should be followed in patients with severe phenylbutazone and piroxicam poisoning [78].

Gastrointestinal decontamination with activated charcoal should be considered for patients who present soon after a significant ingestion, defined as greater than ten therapeutic doses in adults and more than five adult doses in children [72,73]. Although charcoal hemoperfusion has been used to treat a patient with severe phenylbutazone poisoning who had impaired renal and hepatic function [76], extracorporeal elimination measures are unlikely to be effective because of the high-protein binding and rapid intrinsic elimination of these agents. Multiple-dose charcoal therapy enhances the elimination of therapeutic doses of phenylbutazone by 30% [130] and may be similarly effective for other agents, but the clinical benefit of such therapy after overdose is likely to be limited.

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CHAPTER 132 ■ ENVENOMATIONS

ROBERT L. NORRIS

"Their supreme arrogance, developed over millions of years as masters of their environment, commands respect out of all proportions to their size" [1].

Although made in reference to snakes, this statement could easily apply to any of the vast numbers of venomous creatures on the planet. Few areas of medicine are immersed in such controversy and misperception as the management of envenomations. This chapter provides guidance for the evaluation and management of bites and stings of venomous snakes, spiders, and scorpions indigenous to North America. While the general principles of management of envenomations outlined here may be applicable to other regions of the world, specific approaches, such as indications for and types and doses of antivenoms, vary by region, and local experts should be consulted for advice.

SNAKE ENVENOMATION

All of the terrestrial American venomous snakes belong to one of two families: Viperidae (subfamily Crotalinae, or pit vipers) and Elapidae (or coral snakes). Venomous snakes are native to every state of the United States except Alaska, Hawaii, and Maine.

Pit Viper Envenomation

At least 99% of venomous snakebites in the United States are inflicted by pit vipers [2]. The pit vipers of North America include the rattlesnakes (genera *Crotalus* and *Sistrurus*), and the cottonmouth water moccasins, copperheads, and cantils (*Agkistrodon* spp). These snakes are characterized by paired, pitlike heat receptors (foveal organs) located on the anterolateral aspects of the head. These receptors aid the snake in aiming its strike and likely function in determining the quantity of venom to be injected [3,4].

Pit viper venoms contain numerous enzymatic components and a number of nonenzymatic, low-molecular-weight polypeptides [3–5]. Venom compositions vary not only from species to species, but from snake to snake within a species, and even in an individual snake depending on its age, size, health, and other factors [3,4]. In general, the most serious envenomations in North America are caused by the rattlesnakes (particularly *Crotalus* spp), with cottonmouth water moccasin (*Agkistrodon piscivorus* ssp) bites being less severe and copperhead (*A. contortrix* ssp) bites causing predominantly local findings with little serious systemic toxicity.

The major enzymes in pit viper venoms include hyaluronidase (spreading factor), phospholipase A (responsible for cell membrane disruption), and various proteases (causing local tissue destruction) [4,5]. Venom metalloproteinases, termed *disintegrins*, result in disruption of vascular integrity [6]. Despite the impressive toxicity of such enzymes, the nonenzymatic, low-molecular-weight polypeptide fractions appear to be up to 20 times more lethal, on a weight-for-weight basis, than crude venom [7]. The toxicity of pit viper venom is enhanced by release of various autopharmacologic compounds from damaged tissue (e.g., histamine, bradykinin, and serotonin) [4].

Clinical Manifestations

Envenomated patients typically experience moderate-to-severe pain at the bite site within 5 to 10 minutes. The pain is often described as burning and may radiate along the bitten extremity. Swelling at the bite site soon follows and may progress along the entire extremity within hours. There is often local ecchymosis because of disruption of blood vessels. A persistent bloody effluent from the wound suggests the presence of snake venom anticoagulants. Rapid lymphatic absorption of venom may lead to impressive, early lymphangitis and regional adenopathy [3].

Within the first 24 to 36 hours, hemorrhagic bullae or serum-filled vesicles may develop at the bite site and along the bitten extremity. These are less common in bites treated early with adequate amounts of antivenom [4,7]. Petechiae or purpura may also be present.

Systemic manifestations of pit viper envenomation can involve virtually any organ system. Nausea and vomiting are common and may appear early with severe bites [7]. Weakness, diaphoresis, fever and chills, dizziness, and syncope may also occur [3,4]. Some patients experience a minty, rubbery, or metallic taste in their mouth and hypersalivation [4,7]. Muscle fasciculations or paresthesias of the scalp, face, tongue, or digits indicate a moderate-to-severe envenomation. Systemic coagulopathy can lead to bleeding at any anatomic site, including the gastrointestinal, respiratory, genitourinary, and central nervous systems, although clinically significant bleeding is uncommon following bites in North America [3,7].

Alterations in heart rate and blood pressure may occur. Early hypotension is usually due to pooling of blood in the pulmonary and splanchnic vascular beds, whereas delayed shock is due to blood loss, third spacing of intravascular volume, and hemolysis [3,4,8]. Pulmonary edema can occur in severe envenomations, and is secondary to disruption of pulmonary vasculature intimal linings and pooling of pulmonary blood [3,5].

Multifactorial renal failure may occur, but is uncommon. Contributing factors include hypotension; hemoglobin, myoglobin, and fibrin deposition in renal tubules; and direct venom nephrotoxicity [3,7].

Muscle weakness may be seen after bites by some rattlesnakes that possess phospholipase A_2 neurotoxins in their venoms, such as the eastern diamondback rattlesnake (*Crotalus adamanteus*) [9] or some specimens of the Mohave rattlesnake (*Crotalus scutulatus*) [10]. Neuromuscular respiratory failure is rare, but can occur in severe bites by the Mohave rattlesnake in certain geographic locations [7].

Snake venoms do not appear to cross the blood–brain barrier to any significant extent, and rare findings such as seizures and coma are secondary to hypotension, hypoxia, or intracranial bleeding [2].

Diagnostic Evaluation

Important aspects of the history include details of the incident (such as type and size of snake if known, time and number of bites, and methods of first aid applied) and the patient's medical

TABLE 132.1

CLINICAL GRADING SCALE AND RECOMMENDED CROFAB® DOSAGES FOR NORTH AMERICAN PIT VIPER ENVENOMATION[a]

Severity grade	Nonenvenomation	Mild	Moderate	Severe
Fang marks	±	+	+	+
Pain	None	Mild to moderate	Severe	Severe
Edema (proximal extent)	None	Minimal (0–15 cm)	Moderate (15–30 cm)	Severe (> 30 cm)
Erythema	None	+	+	+
Ecchymosis	None	±	+	+
Systemic signs or symptoms	None	None	Mild	Moderate to severe
Laboratory values	Normal	Normal	Mildly abnormal	Very abnormal
Initial CroFab dose (number of vials)[b]	0	0 (if no progression) 4–6 (if progressing)	4–6	6[c]

[a]Not applicable to coral snake envenomations or envenomation by snakes outside of North America.
[b]CroFab® (BTG International Inc., West Conshohocken, PA)—If findings of envenomation progress during the first hour following the initial dose, the dose should be repeated. Once stabilization occurs, two vials are given every 6 hours for three additional doses (see text).
[c]Larger doses may be required in some cases with acute, life-threatening envenomation.

history (including any prior snakebites, medications, allergies, and tetanus immunization status).

Pit viper envenomation is a true emergency with potential for multisystem involvement. The severity of the bite must be assessed, and the clinical severity grading scale in Table 132.1 may be useful in evaluating most pit viper bites [4]. Approximately 20% of bites by U.S. pit vipers result in no envenomation ("dry bites") [4,7,11]. It must be understood, however, that severity can progress rapidly, and the patient must be frequently reevaluated for a worsening clinical condition. Good clinical judgment is more important than overreliance on grading scales. Consultation with an authority in the area of toxinology is prudent.

Puncture-wound patterns can be misleading in the diagnosis of snakebite. Occasionally, there is only a single puncture wound or many tiny punctures [12]. A dry bite may or may not have fang puncture marks, but there is no more pain than would be expected from simple puncture wounds. Envenomation is confirmed by the presence of local tissue effects (particularly progressive swelling), systemic effects, and/or laboratory abnormalities.

Essential laboratory studies include a complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine, prothrombin time or international normalized ratio, fibrinogen, fibrin degradation products, and urine analysis. Blood for type and screening should also be sent for evaluation as soon as possible as direct venom effects and antivenom effects may interfere with this process later [13]. Also helpful are creatine phosphokinase as a measure of muscle damage and intracompartmental pressure measurements in patients with suspected compartment syndrome. Obtain a chest radiograph, arterial blood gases, and an electrocardiogram as clinically indicated.

Occasionally, the history and diagnosis may be unclear, especially in children [14]. When patients present without having seen a snake and have no findings other than puncture wounds and mild pain, the differential diagnosis includes a dry bite, bite by other animal or arthropod (e.g., nonvenomous snake, centipede, or spider), and puncture wounds from inanimate objects (e.g., thorns).

Management

First-aid efforts are best limited to reassuring the victim, immobilizing and splinting the extremity at heart level, and transporting the victim as quickly as possible to a hospital.

Previously recommended first-aid measures including incision, suction, constriction bands pressure immobilization, tourniquets, packing of the extremity in ice, or application of electric shocks should be avoided as they are ineffective and may result in further complications [15–17].

Two large-bore intravenous (IV) lines infusing normal saline should be established, preferably in sites other than the bitten extremity, and blood work sent to the laboratory. Continuous cardiac and pulse oximetry monitoring are indicated, and oxygen is administered if hemoglobin saturation is low or if the patient is experiencing any respiratory distress. Any devices applied in the field in an attempt to limit venom spread should be left in place until an IV line is established.

Management of significant pit viper envenomation centers on the judicious use of an appropriate antivenom. In North America, antivenom therapy is indicated for victims with progressive local tissue findings or systemic abnormalities (significant systemic symptoms or signs, or laboratory abnormalities [e.g., paresthesias, hypotension, prolongation of prothrombin time or international normalized ratio, hypofibrinogenemia, or thrombocytopenia]) (see Fig. 132.1). Controversy exists, however, on the use of antivenom for copperhead (*A. contortrix*) bites presenting with progressive soft-tissue swelling in the absence of systemic abnormalities. Given that most such bites do well with conservative therapy alone [7], the cost–benefit ratio of giving antivenom in these cases is currently unclear and requires further research [18,19].

Antivenom Administration

If possible, informed consent should be obtained before antivenom administration. Antivenom should be administered in a closely monitored setting. Epinephrine and endotracheal intubation equipment should be immediately available at the bedside during antivenom administration, and a physician should be in attendance to observe and manage any acute adverse drug effects that may develop.

In the United States there is currently a single commercially available antivenom for pit viper bites—CroFab® Crotalidae Polyvalent Immune Fab, Ovine (BTG International Inc., West Conshohocken, PA). This antiserum contains purified Fab immunoglobulin fragments from sheep immunized with one of four different pit viper venoms. It comes in a lyophilized state and is effective against all North American pit vipers.

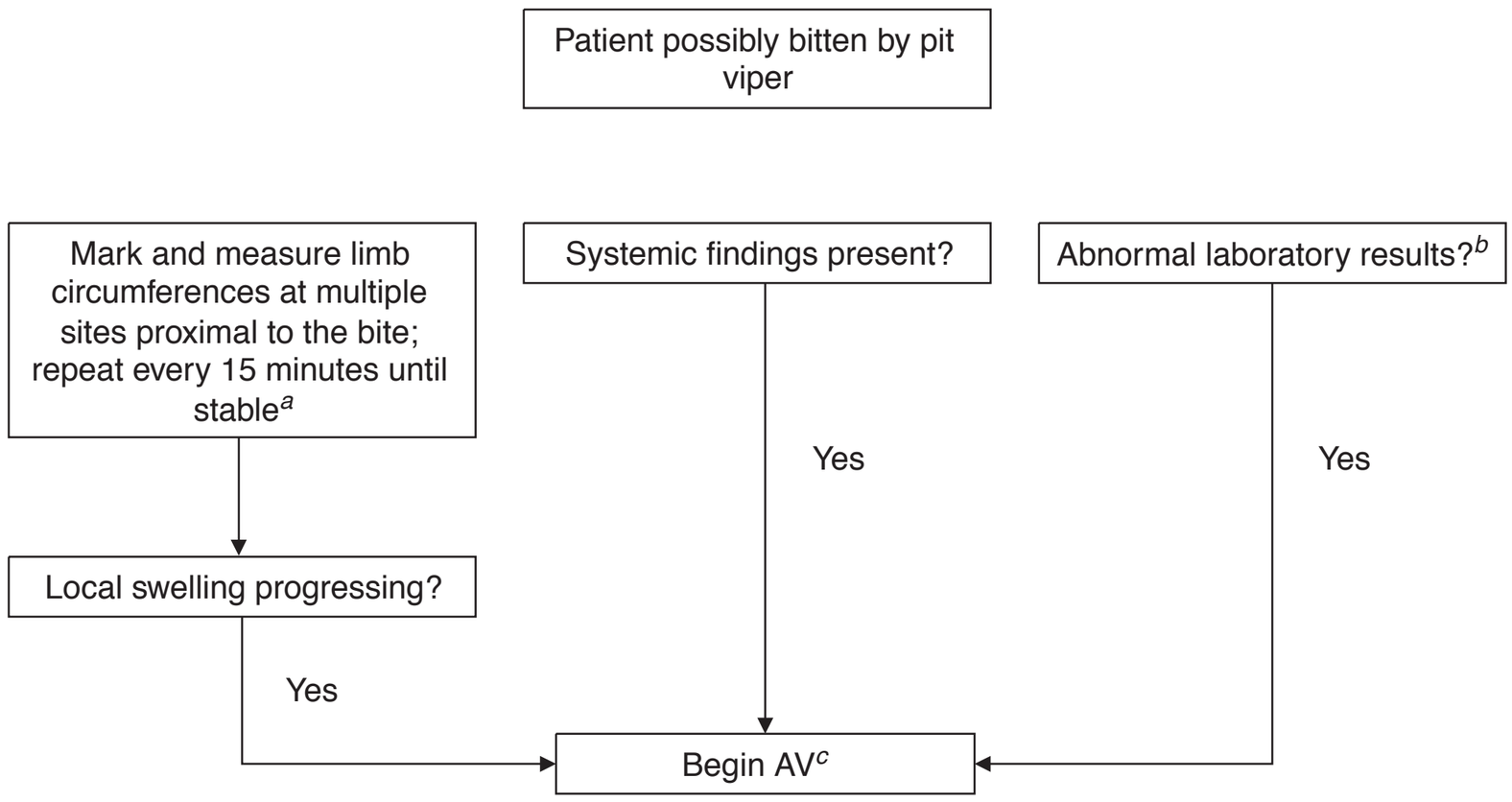

FIGURE 132.1. Guidelines for beginning antivenom therapy for victims of pit viper bite in the United States (see text for details). [a]Keep extremity at heart level, being careful to differentiate redistribution of edema (with changing limb position) from progression of severity of swelling. [b]Repeat normal lab work every hour for 4–6 hours until AV is started or the decision is made that AV is not necessary (i.e., the bite resulted in no envenomation or a mild, nonprogressive envenomation). [c]Abnormal coagulation studies may not return to normal for 4–6 hours after antivenom administration—time necessary for the body to replete coagulation factors after neutralization of venom. AV, antivenom.

Antivenom should be started as soon as possible after indications for administration are met. Although there are no defined end points in terms of time or dosage for when to withhold antivenom, antivenom is beneficial for treating only findings directly related to continued presence of unbound venom in the circulation (e.g., ongoing coagulopathy). It is ineffective in reversing end-organ damage that has resulted from prior venom effects (e.g., renal failure). The efficacy of antivenom in preventing local wound necrosis is limited, as it cannot reverse local cellular damage once it has been initiated by rapidly acting venom enzymes and nonenzymatic polypeptides [14,20,21]. Any ability to reduce necrosis depends on early administration.

Dosing of CroFab® is based on severity of the bite (see Table 132.1), not on age or size of the patient. The initial dose is four to six vials for patients with signs or symptoms of systemic toxicity or evidence of progressive local venom effects. Each CroFab® vial should be reconstituted with 10 mL of warm sterile water or saline. The total dose to be administered is diluted in 250 mL of crystalloid and infused over 1 hour (starting slowly at the onset of infusion and gradually increasing the rate). During the hour after the initial dose is completed, the patient is monitored for further progression of local effects and systemic symptoms, and laboratory studies are repeated [13]. The starting dose of CroFab® is repeated if venom effects continue to progress. This pattern is continued until the patient stabilizes. Coagulation studies may not normalize after the initial dose, as time is required for repletion of coagulation factors after venom neutralization, but they should show evidence of improvement [22,23]. After stabilization, two vials of CroFab® are administered every 6 hours for three additional doses. Further doses may be needed at the physician's discretion.

Adverse effects of antivenoms, as heterologous serum products, are divided into three major groups: acute allergic and nonallergic anaphylaxis, and delayed serum sickness. Acute reactions most commonly manifest with hives and/or bronchospasm [24], though hypotension and angioedema can also occur. Serum sickness is characterized by pruritus, fever, arthralgias, lymphadenopathy, and malaise, which can occur 1 to 2 weeks after antivenom therapy [3]. The incidence of acute reactions to CroFab® is approximately 15% and serum sickness occurs in approximately 3% of patients [25]. Management of acute reactions centers on rapid diagnosis, temporarily halting the infusion and treating with epinephrine, antihistamines, and steroids (see Chapter 194). Generally, once the reaction is controlled, the antivenom infusion can be restarted, possibly in a more dilute state and at a slower rate. Serum sickness is relatively benign and easily treated with steroids, antihistamines, and nonsteroidal anti-inflammatory drugs until symptoms resolve [26]. Most cases do well with oral prednisone (1 to 2 mg per kg per day) until symptoms resolve, followed by a taper over another week.

Supportive Measures

Venom-induced hypotension should be treated with antivenom and volume expansion. If organ perfusion fails to respond promptly with crystalloid infusion (1 to 2 L in an adult and 20 to 40 mL per kg in a child), administration of albumin is advisable as this agent is likely to stay in the leaky vascular system for longer periods of time [4,8]. Pressors should be used as a last resort [4].

Although pit viper envenomation can result in significant coagulopathies, the incidence of clinically significant bleeding in the United States is low [13,27]. Management of coagulopathy in patients with evidence of clinically significant bleeding, other than microscopic hematuria or minor gingival bleeding, may require administration of packed red blood cells, platelets, fresh-frozen plasma, and/or cryoprecipitate [4,28]. There is limited experience using recombinant factor VIIa for severe coagulopathy following rattlesnake bite [29]. It is important to begin antivenom therapy before the infusion of such products to avoid adding fuel to an unabated consumptive coagulopathy.

Therapy to prevent acute renal failure includes ensuring adequate hydration and monitoring urinary output. Hemoglobinuria and myoglobinuria are treated in standard fashion. If renal failure occurs, dialysis may be required, although it does not remove circulating venom components [4,7].

Although steroids are useful in the management of adverse reactions to antivenom (see previous discussion), there is no role for them in the primary management of snake envenomation.

Wound Care and Surgery

Wound care begins with cleaning the bite site with a suitable germicidal solution and covering it with a dry, sterile dressing. As soon as antivenom has been started, if indicated, the extremity should be elevated in a well-padded splint in a position of function with cotton between the digits [3,4]. Antibiotics are unnecessary unless field management involved incisions into the bite site [30] or the wound becomes clinically infected. Tetanus immunization status should be updated as necessary.

Intact hemorrhagic blebs and bullae should be protected. If ruptured, they should be unroofed after any attendant coagulopathy has been reversed [7,31]. Further debridement may be necessary if there is significant tissue necrosis. The use of hyperbaric oxygen therapy to treat these wounds has yet to be fully studied [4,32]. Physical therapy is important in returning the extremity to functional capacity.

The role of surgery in the primary management of pit viper envenomation is very limited. The speed with which snake venom is absorbed makes routine excision of the bite site fruitless [33], and routine exploration of the site does nothing to mitigate systemic effects of venom, may worsen the overall outcome by adding surgical trauma, and prolongs hospitalization [4].

The incidence of compartment syndrome after snake envenomation appears low despite the frequently impressive local findings of bitten extremities [34,35]. Myonecrosis that occurs is usually due to direct venom effects and rarely vascular compromise from elevated intracompartmental pressures [21,34,35]. In combined series of nearly 2,000 victims of pit viper envenomation, only 4 patients required fasciotomy; each of these patients received inappropriate ice treatment or inadequate antivenom [34,35]. If there is concern about an impending compartment syndrome, intracompartmental pressures should be checked using any standard technique. If pressures exceed 30 to 40 mm Hg and remain elevated for more than 1 hour despite appropriate antivenom administration, limb elevation and possibly mannitol infusion (1 to 2 g per kg in a normotensive patient), fasciotomy may be required [35,36]. While some evidence suggests that fasciotomy may actually worsen local myonecrosis [37], unabated elevation of intracompartmental pressures can have disastrous effects, such as debilitating neuropathy [38], and fasciotomy may still be required. Whenever possible, informed consent should be obtained prior to proceeding with fasciotomy.

Disposition and Outcome

Patients with apparent dry bites can be discharged from the emergency department if they remain asymptomatic with normal laboratory values (repeated prior to discharge) after 8 hours of observation [39]. The envenomated patient can be discharged from the hospital when all venom effects have begun to resolve and when antivenom therapy is complete, which is usually within 48 hours after admission. At the time of discharge, every patient should have appropriate follow-up arranged for continued wound care and physical therapy, and should be warned about the symptoms of serum sickness. If such symptoms occur, the patient should seek medical care promptly.

Venom-induced coagulopathy and thrombocytopenia may recur anytime up to 14 days after the last dose of antivenom [40]. Therefore, patients should be followed closely for this phenomenon after discharge from the hospital. If there is evidence of clinically significant bleeding on follow-up or if the laboratory coagulopathy is severe, additional antivenom can be considered, although its efficacy at reversing delayed recurrence of coagulopathy appears to be reduced and the need to treat asymptomatic coagulopathy during recovery is controversial [22,23,40]. Nevertheless, patients who developed coagulopathy during the acute phase of envenomation should be warned to avoid elective procedures and risky activities (such as contact sports) for at least 2 weeks.

The historical mortality rate for patients treated with antivenom in the United States was 0.28%, compared to 2.61% for patients not receiving antivenom [41]. The impact of CroFab® on mortality rates remains to be determined. Death after pit viper poisoning is most likely to occur 6 to 48 hours after envenomation [41,42]. Fewer than 17% of deaths occur within 6 hours and fewer than 4% within 1 hour [41,42]. The major reasons for poor outcome in pit viper envenomation are delay in presentation, inadequate fluid resuscitation, inappropriate use of vasopressors, and delay in administration or inadequate dosing of antivenom [2,43]. The incidence of upper-extremity functional disability after pit viper envenomation is at least 32% [44], and may be higher when careful, objective functional measurements are obtained [45].

Coral Snake Envenomation

There are fewer than 100 coral snake bites reported in the United States each year [46]. The U.S. coral snakes include the eastern coral snake (*Micrurus fulvius*), the Texas coral snake (*Micrurus tener*), and the Sonoran coral snake (*Micruroides euryxanthus*). Mexico boasts 15 *Micrurus* species as well as the Sonoran coral snake [47]. Native U.S. coral snakes can be identified by a characteristic red, yellow, and black banding pattern, with the red and yellow bands contiguous and the bands completely encircling the body. This color pattern does not, however, reliably identify coral snakes south of Mexico City [48]. Coral snakes lack the pitlike heat-receptor organs of pit vipers. While only 40% of coral snake bites result in envenomation because of their much less effective venom-delivery mechanism (small fangs fixed in an upright position on the anterior maxillae) [4,49], it has been estimated that one large coral snake is capable of delivering enough venom to kill four to five humans [50,51]. In the United States, it appears that the severity of envenomation tends to be greatest with the eastern coral snake (*M. fulvius*), less with the Texas coral snake (*M. tener*) and least with the Sonoran coral snake (*Micrur. euryxanthus*) [4,52].

Clinical Manifestations

Coral snake venoms are primarily neurotoxic; low-molecular-weight polypeptides in the venom are capable of inducing nondepolarizing, postsynaptic blockade at neuromuscular junctions [3,53]. There are few local findings at the bite site, and the onset of systemic symptoms may be delayed for many hours [3,49,54]. Fang marks may be small and difficult to detect [55], with variable pain and little swelling at the site [54]. The patient may experience local paresthesias that may radiate proximally and be associated with muscle fasciculations [54,56]. The earliest systemic findings may include alteration of mental status [3,57]. Nausea and vomiting may occur, along with increased salivation [3,49]. Bulbar-type paralysis can occur as early as 90 minutes after the bite and progress to peripheral paralysis [4]. Findings may include extraocular muscle paresis, ptosis, pinpoint pupils, dysphagia, dysphonia, slurred speech, and laryngeal spasm [49,54,56]. Death from coral snake envenomation has been reported because of respiratory failure or cardiovascular collapse [4].

Diagnostic Evaluation

The important history is similar to that obtained in victims of pit viper bites. In areas where coral snakes coexist with harmless coral snake mimics, it is helpful if the color pattern of the offending snake can be recalled.

The clinical grading scale outlined for pit viper envenomation does not apply to coral snake bites because of the paucity of local findings and the potential delay in the onset of systemic symptoms [4]. There are no characteristic changes in routine laboratory tests in coral snake envenomation [2].

The differential diagnosis of coral snake envenomation is usually limited to bites by other brightly colored snakes, such as milk snakes (*Lampropeltis* sp). With these harmless coral snake mimics, the red and yellow bands are separated by black bands, and the bands do not completely encircle the body. The simple rhyme "red on yellow, kill a fellow; red on black, venom lack" is applicable only to snakes found north of Mexico City [48]. The remainder of the differential diagnosis is the same as for pit vipers.

Management

Rapid transportation to a hospital is of utmost priority following coral snake bites [2]. In Australia, where all native venomous snakes are elapid relatives of the coral snake, a potentially beneficial first-aid intervention is use of a pressure-immobilization wrap. In this technique, the entire bitten extremity is firmly wrapped with an elastic or crepe bandage and splinted [58]. The wrap is applied snuggly—as tightly as for a sprained ankle [58]—and it is important that the extremity be kept as immobile as possible and the patient carried to medical care [59]. One small animal study has demonstrated apparent benefit of the technique in prolonging survival following coral snake venom injection [60].

As with pit viper bites, attention is initially directed to the patient's airway, breathing, and circulatory status. Supplemental oxygen should be administered, cardiac and pulse oximetry monitoring established, and at least one IV line should be started. Impending respiratory failure is suggested by cyanosis, trismus, laryngeal or pharyngeal spasm, increased salivation, or any sign of cranial nerve paralysis [54]. If any of these findings is present, prophylactic intubation is indicated to prevent aspiration. Once the airway and respiratory status are addressed, a more complete physical examination is performed. Any swelling should be documented and observed for progression.

Antivenom Therapy

As with most venomous snakebites, definitive management of significant *Micrurus* bites should center on the use of appropriate antivenom. However, the only approved antivenom for coral snake bites in the U.S., Antivenin (*Micrurus fulvius*) (Wyeth Laboratories Inc., Marietta, PA) has been discontinued with remaining stocks due to expire in October 2011. It is possible that another pharmaceutical company may resume coral snake antivenom production for the U.S. Research into the use of an alternative foreign-produced antivenom for U.S. coral snake bites is also under way. (Updates on this topic can be obtained by contacting regional poison control centers.) If an effective coral snake antivenom is available, it should be administered in a monitored setting (with epinephrine available), in consultation with an expert in snake venom poisoning, and with informed consent if possible. Antivenom administration to any patient clearly bitten by a positively identified *Micrurus* specimen, even in the absence of signs or symptoms, has been recommended given that once signs or symptoms begin to appear, it may be difficult to reverse or halt their progression [49,54]. This is likely unnecessary, however, if the offending snake was a Texas coral snake (*M. tener*) [52].

There is no antivenom for the Sonoran coral snake (*Micruroides. euryxanthus*), but the venom of this snake is much less toxic, and there have been no reported deaths after its bite [4,57]. Management of any coral snake bite, in the absence of available antivenom, is entirely supportive. Airway protection and ventilatory support may be required for days following *Micrurus* bites [54], but with modern intensive care, the prognosis should be good nonetheless.

Wound Care

The wounds from a coral snake bite should be washed with a germicidal solution and tetanus prophylaxis updated as necessary. Prophylactic antibiotics are not indicated.

Disposition and Outcome

All patients with potential coral snake bites should be admitted to an intensive care unit for at least 24 hours for close monitoring regardless of symptoms or antivenom requirement [61]. The projected case-fatality rate in untreated cases is up to 10% [49]. Total resolution of all signs or symptoms (e.g., weakness) may take several weeks [54,56].

Exotic (Imported) Snake Envenomation

Exotic venomous snakes are commonly kept in zoos, museums, and sometimes by private individuals in "underground zoos." Occasionally, they may be inadvertently found in imported goods and produce. If the setting of a victim of exotic venomous snakebite, every effort should be made to correctly identify the snake. This can be done by contacting available zoo personnel or biologists. The treating physician should then call a regional poison control center for assistance (1-800-222-1222). These centers have access to a national listing of available sources of exotic antivenoms in stock in the United States. Antivenoms tend to be quite specific for the species against which they protect, and should be used only if there is clear evidence of their efficacy against the offending species. Sound supportive care, combined with an appropriate antivenom when available, should offer the best chances of an optimal outcome.

SPIDER ENVENOMATION

While many spiders are capable of biting humans, only two types are medically significant in North America: the widow spiders (*Latrodectus* sp) and the recluse spiders (*Loxosceles* sp).

Widow Spider Envenomation

Of five known species of widow spider in the United States, the black widows (*Latrodectus mactans*, *Latrodectus hesperus*, and *Latrodectus variolus*) are the best known [62]. The female black widow is dark black and oval shaped, with a characteristic ventral red, orange, or yellow (hourglass-shaped) marking on the abdomen. The body is approximately 1.5 cm long and the leg span up to 4 cm. The other two species in the United States are the red-legged widow or red widow (*Latrodectus bishopi*) and the brown widow (*Latrodectus geometricus*) [62]. Widow spiders are found in all of the 48 contiguous states and Hawaii [63], and are responsible for most of the very rare spider-related deaths in North America. Only the female is dangerous to humans; the male, a nondescript and much smaller brown spider, is incapable of delivering a bite through human skin [64].

The venom of all species of widow spiders is similar in composition and toxic effects [65]. The most deleterious venom component is alpha-latrotoxin, a potent neurotoxin that acts primarily at the neuromuscular junction [64]. The venom initially stimulates the release of neurotransmitters (acetylcholine, epinephrine, and norepinephrine) and then blocks

neurotransmission by depleting synaptic vesicles [64–66]. It does not cause dermonecrosis or hemolysis [67].

Clinical Manifestations

The widow spider bite may be unnoticed by the patient or may be felt as a pinprick [65]. The bite site may be visible, with tiny fang marks approximately 1 mm apart, and the area may be slightly warm and blanched with a surrounding erythematous, indurated zone [68]. Swelling is minimal [69].

Significant symptoms usually appear 10 minutes to 2 hours after envenomation [42,68]. The most prominent symptom is pain. It begins at the bite site as a dull ache and spreads first to local muscle groups and then to larger regional muscle groups of the abdomen, back, chest, pelvis, and lower extremities. Muscle spasms and rigidity are classically present [68,70,71]. Spasms of abdominal musculature can mimic an acute abdomen, though rebound tenderness is absent. Chest muscle rigidity may produce respiratory distress [70,71]. The respiratory rate increases, and there may be associated tachycardia and hypertension. Pain severity typically peaks after several hours [72]. In patients at risk, the hypertension can lead to cerebrovascular accidents, exacerbation of congestive heart failure, and myocardial ischemia [64,65,73]. Cardiac dysrhythmias and priapism have been reported [68,74].

Associated signs or symptoms include diaphoresis, fever, headache, nausea and vomiting, restlessness and anxiety, periorbital edema, and skin rash [68,70]. Deep tendon reflexes may be increased [71].

Diagnostic Evaluation

The history surrounding a widow spider bite is confusing if a spider was not seen. A high index of suspicion should be maintained in patients presenting with compatible complaints. It is important to obtain a medical history, such as hypertension, pregnancy status, allergies, and tetanus immunization status. The physical examination entails a general screening with particular attention to the vital signs, which should be checked at frequent intervals. Close examination for a bite site may be productive.

There are no diagnostic changes in routine laboratory tests in widow spider envenomation. An elevation in white blood cell count and serum creatine phosphokinase values may be seen [75], and proteinuria has been reported [76]. An electrocardiogram and chest radiograph should be obtained as clinically indicated. A pregnancy test should be obtained in women of childbearing age as widow spider venom is a potent abortifacient.

The differential diagnosis includes envenomations by other arthropods, such as neurotoxic scorpions (see the section "Scorpion Envenomation"), and systemic disorders, such as acute rhabdomyolysis, heat cramps, heat stroke, neuroleptic malignant syndrome, tetanus, and strychnine poisoning. Various causes of abdominal pain and rigidity should be considered.

Management

Although there are no specific first-aid measures effective in widow spider bites, temporary application of ice to the bite site may reduce pain [64]. Adequate airway, respiration, and circulatory status should be ensured. After providing oxygen, cardiac and pulse oximetry monitoring, and starting an IV line, attention should be directed to alleviating painful muscle spasms. Although there are anecdotal reports of successful treatment of painful muscle spasms with IV calcium gluconate [69,70], larger case series have found it completely ineffective [62]. Similarly, methocarbamol has met with only limited anecdotal success [69]. Benzodiazepines and opioids can be administered in usual doses and are often most effective when administered in combination [62].

Hypertension usually responds to bed rest, muscle relaxants, analgesics, and sedation [64]. Specific antihypertensive agents can be used if necessary [64].

Antivenom

A specific, equine, whole-immunoglobulin widow spider antivenom, Antivenin (*L. mactans*) (manufactured by Merck & Co., Inc., West Point, PA) is effective regardless of which *Latrodectus* species is involved [77]. Indications for antivenom use remain controversial [78], but are generally accepted to include a patient who is severely envenomated, is pregnant or in labor, or has a history of cardiovascular disease or other major medical problems and evidence of significant envenomation despite benzodiazepine and opioid therapy [68,71,72]. Antivenom is very effective in relieving pain, but its use solely for this purpose is controversial [69,79]. *Latrodectus* antivenoms manufactured by other countries appear to be effective in managing bites by widow spiders native to the United States [80,81].

As with snake antivenom administration, informed consent should be obtained and antivenom administered in a monitored setting with epinephrine available at the bedside. Prior to antivenom administration, the patient can be premedicated with IV antihistamines (H_1 and H_2 blockers), though the benefit of such an approach is unproven. The antivenom can be given intravenously (one reconstituted vial further diluted in 50 to 100 mL of normal saline, administered over 30 minutes) or intramuscularly (one reconstituted vial in the anterolateral thigh) [82], with the physician in immediate attendance to observe for any sign of adverse drug events. The IV route is preferred if the patient is in shock or younger than 12 years [82]. The dosage is the same for children [64,70]. One vial is generally adequate, but a second vial can be administered if necessary [70,72]. Signs or symptoms should completely resolve within a few hours of antivenom administration [70,72].

The types of adverse drug events seen with widow spider antivenom are the same as for snake antivenoms, but the risk of serum sickness may be less because of the smaller total amount of foreign protein infused [72].

The clinical course of most patients with widow spider envenomation is benign [68], but significant pain and spasms can persist for 2 to 3 days [72,79]. Most healthy adults do well with supportive measures and adequate administration of parenteral benzodiazepines and opioids [68].

Disposition and Outcome

Patients can be discharged from the hospital when signs or symptoms of envenomation have been significantly controlled, though it may be best to admit and observe younger children. Patients should be given analgesics and muscle relaxants, prescribed bed rest, and instructed to return if they worsen. The mortality rate from widow spider envenomation in the United States is less than 1% [65,68]. Recovery from widow spider envenomation may sometimes be slow, with weakness, fatigue, paresthesias, headache, and insomnia persisting for several months [64].

Recluse Spider Envenomation

Of the 13 species of recluse spider (*Loxosceles* spp) found in the United States [83], the brown recluse (*Loxosceles reclusa*) is best known [84]. It is characterized by a violin-shaped marking on the dorsal aspect of the cephalothorax and three pairs of

eyes, in contrast to the four pairs found in most spiders. The adult body is 10 to 15 mm long and the legs span 2 to 3 cm. Both the male and female spiders are dangerous [72].

The brown recluse is found throughout the southern, south-central, and midwestern United States; other species are found in the western part of the country [62]. While recluse spiders may cause severe dermonecrosis (necrotic arachnidism), the majority of bites actually result in insignificant lesions [85].

The venoms of the different species of recluse spider have similar toxic effects [86]. They contain a number of different proteins, most of which demonstrate enzymatic activity [87]. Sphingomyelinase D is likely responsible for the venom's cytotoxic and hemolytic effects [88–90]. Venom activation of the complement cascade induces a series of autopharmacologic changes that amplify toxicity to a variable degree in victims [91].

The cutaneous changes seen after a recluse spider bite are initiated by venom-induced endothelial damage in small dermal vessels that become occluded with microthrombi, producing vascular stasis and infarction [92]. Polymorphonuclear leukocytes are attracted to the site via a chemotactic response and propagate the inflammatory, necrotic reaction [92,93]. Accumulation of polymorphonuclear leukocytes at the site appears to be a vital component of the dermonecrotic response and is related to complement activation [93].

Clinical Manifestations

The clinical course of recluse spider envenomation varies from a mild temporary irritation at the bite site to a rare, severe, potentially fatal outcome [84]. The bite is occasionally felt as a mild stinging sensation, although it may go completely unnoticed [94]. During the next several hours, there may be pruritus, tingling, mild swelling, and redness or blanching at the bite site [95]. Variable degrees of local pain and tenderness due to local vasospasm and ischemia occur within 2 to 8 hours [95,96]. At 12 to 18 hours, a small central vesicle (clear or hemorrhagic) often develops at the site and is surrounded by an irregular zone of erythema or ecchymosis and edema, which may have a distinct gravitational distribution around the central lesion [97]. The vesicle ruptures, and the erythema gives way to violaceous discoloration [96]. In 5 to 7 days, the bite site undergoes aseptic necrosis (i.e., dry, gangrenous slough), with the center becoming depressed below the normal level of the skin, and a black eschar forms. The eschar later sloughs, leaving an open ulcer that heals in weeks to months [96]. Bites to fatty regions of the body tend to be more severe, with undermining of the skin and more extensive scarring [96]. Necrosis rarely involves deeper structures such as nerves, muscles, tendons, or ligaments [98]. Lesions destined to develop significant necrosis usually demonstrate early evidence of local ischemia [95].

Systemic (viscerocutaneous) loxoscelism is rare, but can be rapidly progressive and severe, particularly in children [72]. Systemic symptoms generally start 24 to 72 hours after the bite and occasionally occur before cutaneous findings become impressive [99]. Symptoms are often flulike, with fever, chills, headache, malaise, weakness, nausea and vomiting, myalgias, and arthralgias [96]. Hemolytic anemia with hemoglobinemia, hemoglobinuria, jaundice, thrombocytopenia, disseminated intravascular coagulation, acute renal failure, seizures, and coma have been reported [72]. The severity of systemic symptoms is directly related to the quantity of venom deposited, but does not necessarily correlate with the severity of cutaneous changes [97].

Diagnostic Evaluation

It is rare for a victim of a *Loxosceles* bite to see the offending spider because the bite is relatively painless and a large percentage of bites occur while the victim is asleep [85]. Because the spider is rarely available for identification, determining the cause of early lesions is difficult [97], and the diagnosis of spider bite is usually presumptive. The working diagnosis should be cutaneous necrosis if the precise cause is unknown and necrotic arachnidism if a biting spider was seen but not identified.

An examination for evidence of systemic loxoscelism should be performed. The severity of any lesion present should be assessed and any evidence of secondary infection noted. There are no characteristic changes in routine laboratory tests in recluse spider envenomation. In patients with severe envenomation, laboratory studies should include a complete blood cell count and urinalysis [96]. If there is any evidence of consumptive coagulopathy, hemolysis, or hemoglobinuria, further studies should include prothrombin time and partial thromboplastin time, electrolytes, blood urea nitrogen, and creatinine, and a specimen should be sent for blood typing and screening. The white blood cell count may be as high as 20,000 to 30,000 per mm^3, and the hemoglobin may fall to as low as 4 g per dL [67,72,96]. Serial complete blood cell counts and urinalyses should be obtained in patients with significant lesions or systemic loxoscelism [96].

There is no commercially available test to definitively diagnose recluse spider envenomation. The differential diagnosis for *Loxosceles* envenomation includes bites or stings by other arthropods (e.g., other spiders, ticks, scorpions, ants, fleas, kissing bugs, and biting flies), superficial skin infections (especially methicillin-resistant *Staphylococcus aureus*), cutaneous anthrax, diabetic ulcers, plant puncture wounds, sporotrichosis, toxic epidermal necrolysis, pyoderma gangrenosum, erythema nodosum, erythema migrans, herpes zoster, herpes simplex, erythema multiforme, purpura fulminans, and contact dermatitis.

Management

No commercial antivenoms exist for *Loxosceles* bites in the United States. The majority of cases require only local wound care, including cleansing of the bite site, application of a sterile dressing, immobilization with a well-padded splint, and tetanus prophylaxis as necessary [67]. Frequent local application of ice or cold packs during the first 72 hours to reduce sphingomyelinase D activity is probably beneficial [84]. If an ulcer develops, it should be cleaned several times each day with hydrogen peroxide or povidone–iodine solution [96]. Pruritus can be treated with antihistamines. Antibiotics to prevent secondary cellulitis may be beneficial [84] and should include coverage for methicillin-resistant *S. aureus* [100].

It is important to emphasize to patients that nothing has been proven to decrease the extent of dermonecrosis after these bites and that most lesions heal quite satisfactorily with conservative management alone [67,96,101]. Controversial modalities for managing the wound include the use of steroids, dapsone, colchicine, surgery, hyperbaric oxygen therapy, and topical nitroglycerine application [78,87,102–105]. Routine use of these agents should be avoided until prospective controlled studies prove that benefits outweigh risks.

Early excision of the wound site is contraindicated because it is impossible to predict the ultimate extent and severity of the lesion [87]. Severe-appearing lesions commonly involute and regress spontaneously to leave minimal defects [106]. Surgical procedures that might be required, such as skin grafting, should be postponed at least 6 to 8 weeks to ensure that the necrotic process has been completed and to improve chances of healing [87]. Hyperbaric oxygen therapy may be useful in particularly severe wounds, but this remains unproven [87,107].

Initial management of systemic loxoscelism includes adequate hydration, maintaining electrolyte balance, and

administering nonsalicylate antipyretics and analgesics [67,96]. Although the use of systemic corticosteroids to stabilize red blood cell membranes has yet to be studied in a controlled fashion, an early, short course of therapy may be beneficial in patients with hemolysis. The recommended dose is 1 mg per kg per day of prednisone orally for 2 to 4 days [67]. Blood products are used as indicated to treat anemia or thrombocytopenia [67]. If hemoglobinuria occurs, hydration becomes critically important, and urine output should be maintained at 2 to 3 mL per kg per hour [96]. If renal failure develops, dialysis may be indicated [67,96]. Dialysis does not remove venom or hemoglobin from the circulation, however [96].

Disposition and Outcome

Patients may be discharged from the hospital when systemic effects have resolved. Close follow-up (daily wound checks) should be provided to patients with cutaneous lesions. Although there have been no reports of deaths in patients bitten by positively identified recluse spiders in the United States [72,96], there is risk of death from systemic loxoscelism, especially in children.

SCORPION ENVENOMATION

The only scorpion species of major medical importance that is native to the United States is the bark scorpion (*Centruroides sculpturatus* [formerly *C. exilicauda*]) [108]. This species is found throughout Arizona and immediately surrounding regions of neighboring states [109]. Other closely related *Centruroides* scorpions of medical importance are found in Mexico. The bark scorpion is 13 to 75 mm long and yellow brown in color, with variable striping on the dorsum [109–111], and has a small subaculear tubercle at the base of the stinger [112].

The venom of *C. sculpturatus* is complex. It contains at least five distinct neurotoxins that cause release of neurotransmitters from the autonomic nervous system and adrenal medulla and stimulate depolarization of neuromuscular junctions [113,114]. Its venom contains no major enzymatic components [115].

Clinical Manifestations

Most *C. sculpturatus* stings are minor, with the most serious envenomations occurring in children [116]. The sting usually produces intense pain at the site, although local pain may be absent in children younger than 10 years [110]. Pain or numbness may radiate up the extremity [110]. Soft-tissue swelling and ecchymosis are notably absent [115].

Systemic symptoms may include restlessness or anxiety, uncoordinated neuromotor hyperactivity, oculomotor dysfunction, and respiratory distress related to excess secretions, airway obstruction, and in some cases, noncardiogenic pulmonary edema [116,117]. Hyperactivity may be mistaken for seizures [118]. Supraventricular tachycardia and hypertension have been reported [113], and severe hyperthermia may occur [111]. The duration of symptoms appears to be inversely proportional to age and may persist for up to 30 hours [110].

Local consequences after envenomation by other scorpions in the United States consist of immediate, brief, intense pain; mild soft-tissue swelling; and mild ecchymosis [119]. Systemic manifestations are uncommon, and allergic reactions are rare [77].

Diagnostic Evaluation

Patients stung by scorpions frequently see the offending organism. A general medical history should be obtained, symptoms assessed, and prehospital treatments noted. Vital signs should be frequently monitored. The sting site should be inspected and the patient examined for signs of systemic toxicity.

There are currently no commercial laboratory tests of diagnostic benefit in patients suspected of *C. sculpturatus* envenomation. The white blood cell count and serum glucose may be elevated [113]. Increases in serum amylase, creatine phosphokinase, and renal function studies, mild abnormalities in coagulation parameters, and cerebral spinal fluid pleocytosis have been reported [117].

The diagnosis is usually not difficult because adults often relate the history of a scorpion sting; in children, the clinical picture after a *C. sculpturatus* sting is rarely confused with other diagnoses [110]. The differential diagnosis includes central nervous system infection, widow spider envenomation, tetanus, dystonic drug reaction, intoxication (e.g., pesticides, anticholinergics, sympathomimetics, xanthines, propoxyphene, and strychnine), drug withdrawal, anaphylaxis, and seizure disorder.

Management

The majority of *C. sculpturatus* stings can be treated with cold compresses and analgesics [113]. Patients with more severe envenomations should receive oxygen and have an IV line established, along with continuous cardiac and pulse oximetry monitoring. The airway should be secured if there are signs of respiratory failure or inability to handle secretions [117]. Anxiety, restlessness, muscular hyperactivity, and moderate hypertension can initially be treated with parenteral benzodiazepines and bed rest [109]. β-Adrenergic–blocking agents have been recommended for hemodynamically significant supraventricular tachycardia [113,114], though caution must be used to ensure that hypertension is not exacerbated because of unopposed α-adrenergic effects. A combined beta-/alpha-blocking agent has theoretical advantages in such scenarios. Antihypertensive agents can be used for severe blood pressure elevation. Narcotics should be avoided because they appear to have a synergistic neurotoxic effect with the venom [120].

At the time of this writing, there were no commercially available antivenoms for scorpion stings in the United States. Recent work, however, demonstrates significant efficacy in the use of scorpion-specific $F(ab')_2$ antivenom (Anascorp, *Centruroides* [scorpion] immune $F(ab')_2$ intravenous [equine], Instituto Bioclon, Mexico) in rapidly reversing the neurotoxic effects, benzodiazepine requirements, and serum venom levels in children stung by bark scorpions in Arizona [116]. The University of Arizona Poison and Drug Information Center should be contacted for updates and availability of this product (phone: 1–800-222–1222). In the absence of available antivenom, the treating physician faced with a severely envenomated victim must rely on sound supportive care in an intensive care setting. Such care may be required for several days [116].

Deaths after a *C. sculpturatus* sting are exceptionally rare [109,113], but the potential for a fatal outcome should not be underestimated, especially in small children and the infirm.

SUMMARY (Table 132.2)

TABLE 132.2

SUMMARY OF HOSPITAL MANAGEMENT RECOMMENDATIONS FOR ENVENOMATIONS IN NORTH AMERICA

Syndrome	Management
Pit viper	
Rattlesnake (*Crotalus* or *Sistrurus* spp), cottonmouth water moccasin, or copperhead (*Agkistrodon* spp)	■ ABCs, O_2, cardiac/pulse oximetry monitoring, two large-bore IV lines, physiologic saline infusion ■ Measure extremity circumferences every 15 minutes during acute phase ■ Laboratory assessment (see text) ■ Update tetanus immunization status as needed ■ No evidence of envenomation—monitor for a minimum of 8 hours [39] ■ Mild envenomation without evidence of progression—no antivenom, admit for monitoring [24] ■ Mild envenomation with progression or moderate-to-severe envenomation (evidence of systemic toxicity [systemic signs or symptoms, or laboratory abnormalities])—administer antivenom (see text) [24] ■ Shock management includes IV physiologic saline boluses (10–20 mL/kg) and antivenom; if refractory, consider albumin [8] and, as last resort, vasopressors [4] ■ Blood products uncommonly required after administration of adequate antivenom [28] ■ If concerned re: compartment syndrome, measure intracompartmental pressures (see text); fasciotomy only for documented increase in pressures unresponsive to elevation of the extremity and antivenom [36] ■ Antibiotics only for evidence of secondary infection (uncommon) [30]
Coral snake	
Texas or Eastern coral snake (*Micrurus* spp)	■ ABCs, O_2, cardiac/pulse oximetry monitoring, at least one large-bore IV line, physiologic saline infusion ■ Early intubation and respiratory support if any evidence of difficulty with breathing or handling secretions [54] ■ Update tetanus immunization status as needed ■ No evidence of envenomation—admit for monitoring (minimum of 24 hours) [61] ■ Evidence of neurotoxicity—administer antivenom if available (see text); if no antivenom available, supportive care only; admit for monitoring until recovered
Sonoran coral snake (*Micruroides euryxanthus*)	■ ABCs, O_2, cardiac/pulse oximetry monitoring, at least one large-bore IV line, physiologic saline infusion ■ Update tetanus immunization status as needed ■ No evidence of envenomation—admit for monitoring (minimum of 24 hours) ■ Evidence of neurotoxicity—admit for monitoring until recovered, supportive care only
Widow spider (*Latrodectus* spp)	■ ABCs, O_2, cardiac/pulse oximetry monitoring, at least one large-bore IV line, physiologic saline infusion ■ Update tetanus immunization status as needed ■ No evidence of envenomation—monitor for 6–8 hours) ■ Evidence of envenomation Mild: analgesics and muscle relaxants (narcotics and benzodiazepines) [62] More severe or high-risk patient (see text): consider antivenom administration with informed consent (see text) [68]
Recluse spider (*Loxosceles* spp)	■ Laboratory assessment (see text) ■ Conservative wound care (cleansing, splinting, debride only clearly necrotic tissue) ■ Update tetanus immunization status as needed ■ Any evidence of infection: broad-spectrum antibiotics (include MRSA coverage) [84,100] ■ Daily wound checks until progressive healing ■ Delay any required skin grafts for 6–8 weeks (see text) [87] ■ If evidence of systemic toxicity: admit, IV fluids, steroids (see text); blood product transfusion and dialysis for renal failure as needed [67,96]
Scorpion	
Neurotoxic scorpion (e.g., *Centruroides sculpturatus*)	■ ABCs, O_2, cardiac/pulse oximetry monitoring, at least one large-bore IV line, physiologic saline infusion ■ Analgesics (nonnarcotic), benzodiazepines [109,120] ■ Update tetanus immunization status as needed ■ If severe: consider antivenom if available, otherwise conservative care [116]
Nonneurotoxic scorpion	■ Analgesics as needed ■ Update tetanus immunization status as needed

ABCs, airway, breathing, circulation assessment and management as needed; O_2, oxygen; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

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CHAPTER 133 ■ HEAVY METAL POISONING

LUKE YIP[□]

This chapter focuses on the aspects of acute poisoning by arsenic, lead, and mercury that are potentially life threatening or may lead to permanent organ damage and hence require immediate, usually intensive, medical care. Reviews of the evaluation and management of asymptomatic exposures and nonacute poisoning can be found elsewhere [1,2].

[□]The views expressed do not necessarily represent those of the agency or the United States.

ARSENIC

Exposure to arsenic may come from natural sources, industrial processes, commercial products, food, or intentionally

administered sources either with a benevolent (acute promyelocytic leukemia [APL] treatment, folk and naturopathic remedies) [3,4] or malevolent intent. Today, acute arsenic poisoning is most commonly the result of an accidental ingestion or the result of a suicidal or homicidal intent.

Pharmacology

Arsenic compounds can be classified into three major groups: inorganic, organic, and arsine gas (AsH_3). The latter is discussed separately. Arsenic compounds can also be classified by their valence state. The three most common valence states are the metalloid (elemental [0] oxidation state), arsenite (trivalent [+3] state), and arsenate (pentavalent [+5] state). In general, the arsenic compounds can be arranged in their order of decreasing toxicity: inorganic trivalent compounds, organic trivalent compounds, inorganic pentavalent compounds, organic pentavalent compounds, and elemental arsenic. Trivalent arsenic is generally two- to tenfold more toxic than pentavalent arsenic. The minimum oral lethal human dose of arsenic trioxide (trivalent) is probably between 10 and 300 mg. Some marine organisms and algae contain large amounts of organic arsenic in the form of arsenobetaine—a trimethylated arsenic compound—and arsenocholine. Arsenobetaine and arsenocholine are excreted unchanged in the urine, with total clearance in about 2 days, and exert no known toxic effects in humans.

The major routes of entry into the human body are ingestion and inhalation. Soluble forms of ingested arsenic are 60% to 90% absorbed from the gastrointestinal (GI) tract. The amount of arsenic absorbed by inhalation is also thought to be in this range. Toxic systemic effects have been reported from rare occupational accidents in which arsenic trichloride or arsenic acid was splashed on worker's skin.

After absorption, arsenic is bound to proteins in the blood and redistributed to the liver, spleen, kidneys, lungs, and GI tract within 24 hours. Clearance from these tissues is dose dependent. Two to four weeks after exposure ceases, most of the arsenic remaining in the body is found in keratin-rich tissues (e.g., skin, hair, and nails).

Both forms of arsenic, arsenite and arsenate, undergo biomethylation in the liver to monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). The methylation process may represent detoxification because the metabolites exert less acute toxicity in experimental lethality studies. The liver's efficiency in methylation decreases with increasing arsenic dose. When the methylating capacity of the liver is exceeded, exposure to excess concentrations of inorganic arsenic results in increased retention of arsenic in soft tissues.

Arsenic is eliminated from the body primarily by renal excretion. Urinary arsenic excretion begins promptly after absorption, and depending on the amount of arsenic ingested, urinary arsenic excretion may remain elevated for 1 to 2 months. After acute intoxication by inorganic arsenic, arsenic is excreted in the urine as inorganic arsenic, MMA and DMA, but their proportion varies with time [5]. During the first 2 to 4 days after the intoxication, arsenic is excreted mainly in the inorganic form. This is followed by a progressive increase of the proportion excreted as MMA and DMA. The time at which arsenic is primarily excreted as its methylated metabolites depends on the severity and duration of the intoxication. Pentavalent arsenic is cleared more rapidly than trivalent arsenic. Because arsenic is quickly cleared from the blood, blood concentrations may be normal, while urine concentrations remain markedly elevated. Renal dysfunction may be a major impediment to normal elimination of arsenic compounds.

Inorganic arsenic can cross the human placenta. This was evident by the high arsenic concentrations found in a neonate following acute maternal arsenic intoxication [6].

There are two major mechanisms by which arsenic compounds appear to produce injury involving multiorgan systems. It is believed that arsenic's overt toxicity is related to its reversible binding with sulfhydryl enzymes, leading to the inhibition of critical sulfhydryl-containing enzyme systems. Trivalent arsenite is particularly potent in this regard. The pyruvate and succinate oxidation pathways are particularly sensitive to arsenic inhibition. Dihydrolipoate, a sulfhydryl cofactor, appears to be a principal target. Normally, dihydrolipoate is oxidized to lipoate via a converting enzyme, dihydrolipoate dehydrogenase. Arsenic reacts with both dihydrolipoate and dihydrolipoate dehydrogenase, preventing the formation of lipoate. Lipoate is involved in the formation of key intermediates in the Krebs cycle. As a result of lipoate depletion, the Krebs cycle and oxidative phosphorylation are inhibited. Without oxidative phosphorylation, cellular energy stores (adenosine triphosphate [ATP]) are depleted, resulting in metabolic failure and cell death.

The other major mechanism by which arsenic is believed to produce cellular injury is termed *arsenolysis*. Pentavalent arsenate can competitively substitute for phosphate in biochemical reactions. During oxidative phosphorylation, energy is produced and stored in the form of ATP. The stable phosphate ester bond in ATP can be replaced by an arsenate ester bond. However, the high energy stored in the arsenate ester bond is wasted because it is unstable and rapidly hydrolyzed. Cellular respiration is stimulated in a futile attempt to restore this wasted energy. In effect, trivalent arsenic compounds inhibit critical enzymes in the Krebs cycle, leading to inhibition of oxidative phosphorylation, and pentavalent arsenic compounds uncouple oxidative phosphorylation by arsenolysis. This results in the disruption of cellular oxidative processes, leading to endothelial cellular damage. The fundamental lesion seen clinically is loss of capillary integrity, resulting in increased permeability of blood vessels and tissue hypoxia, leading to generalized vasodilation, transudation of plasma, hypovolemia, and shock.

In vitro, the effects of arsenic trioxide on repolarizing cardiac ion currents appear to be one of antagonism on both I_{Kr} and I_{Ks} as well as activation of I_{K-ATP}, which maintains normal repolarization [3]. In addition, arsenic trioxide increases cardiac calcium currents and reduces surface expression of the cardiac potassium channel human ether-a-go-go-related gene. The variability in QTc interval prolongation and the onset of ventricular dysrhythmias during arsenic therapy may represent these competing effects.

Clinical Toxicity

The most prominent clinical findings associated with acute arsenic poisoning are related to the GI tract. Some arsenic is corrosive. Acute ingestion may lead to oral irritation and a burning sensation in the mouth and throat. A metallic taste and/or a garlicky odor to the breath have been described, but often are not present. Nausea, vomiting, and abdominal pain are common. The toxic effects of arsenic on the GI tract are manifested as increased peristalsis and profuse watery stools and bleeding. In serious cases, hemorrhagic gastroenteritis may ensue within minutes to hours after acute ingestion. Nausea, vomiting, and severe hemorrhagic gastroenteritis can all lead to profound intravascular volume loss resulting in hypovolemia shock, which is the major cause of mortality and morbidity.

Noncardiogenic pulmonary edema may occur from increased capillary permeability, and cardiogenic pulmonary edema may occur from myocardial depression. Electrocardiogram (ECG) changes associated with arsenic poisoning consist of nonspecific ST- and T-wave changes, sometimes mimicking ischemia or hyperkalemia and QTc prolongation [7–9]. These

TABLE 133.1

ADVERSE DRUG EVENTS ASSOCIATED WITH ARSENIC TRIOXIDE INDUCTION THERAPY

Cardiovascular	QTc prolongation (≥500 msec), torsades de pointes, sudden death, tachycardia
Hematologic	Hyperleukocytosis (10,000–170,000 cells/μL)
Nervous system	Peripheral neuropathy, headache
Metabolic	Hypokalemia, hypomagnesemia, hyperglycemia
APLDS	Fever, pleural or pericardial effusion, pleural infiltrates, respiratory distress, weight gain, musculoskeletal pain
GI	Nausea, vomiting, diarrhea
Dermatologic	Skin rash

APLDS, acute promyelocytic leukemia differentiation syndrome; GI, gastrointestinal.

ECG abnormalities are reported to occur in half the patients with arsenic poisoning, and these ECG changes may be evident from 4 to 30 hours postingestion, persisting for up to 8 weeks.

At least five cases of arsenic-induced polymorphic ventricular tachycardias consistent with torsades de pointes have been reported [8,9]. In all these cases, QTc prolongation was evident on the admission ECG. Except in the case of the patient who presented with cyanosis and cardiorespiratory arrest, peripheral neuropathy was a prominent finding on physical examination at the time of hospital admission, and the polymorphic ventricular tachydysrhythmias were ultimately self-limited. Although these cases were able to document as to when during the hospital course torsades de pointes were observed, the time between arsenic exposure and the onset of cardiac dysrhythmias can only be speculated.

Arsenic was abandoned 30 years ago as an anticancer medicinal, but has attracted renewed attention as a treatment for APL on the basis of impressive results from clinical studies in China and the United States [3]. Arsenic trioxide is licensed for use in patients with relapsed or refractory APL. Induction therapy in APL patients receiving daily median arsenic trioxide infusions of 0.15 mg per kg (range, 0.06 to 0.2 mg per kg) during 1 to 2 hours until bone marrow remission or for a maximum of 60 days has been associated with adverse drug events (Table 133.1) [3]. In patients receiving multiple courses of arsenic trioxide therapy, their QTc intervals returned to pretreatment values before their second course, signifying that arsenic trioxide may not permanently prolong the QTc interval.

Both acute and chronic arsenic poisoning may affect the hematopoietic system. A reversible bone marrow depression with pancytopenia, particularly leukopenia, may occur. However, it is the chronic form that is usually associated with severe hematopoietic derangements. A wide variety of hematologic abnormalities have been described with arsenic poisoning, including anemia, absolute neutropenia, thrombocytopenia, eosinophilia, and basophilic stippling [10]. Anemia is, in part, due to an increase in hemolysis and disturbed erythropoiesis/myelopoiesis with reticulocytosis and predominant normoblastic erythropoiesis. Accelerated pyknosis of the normoblast nucleus, karyorrhexis, is characteristic of arsenic poisoning, and the typical "cloverleaf" nuclei may be evident [11]. Hematologic findings may appear within 4 days after acute arsenic ingestion, and in the absence of any specific therapy, erythrocytes, leukocytes, and thrombocytes were reported to return to normal values within 2 to 3 weeks after discontinuing arsenic exposure.

Neurologic manifestations of arsenic poisoning have included confusion, delirium, convulsions, encephalopathy, and coma [12]. Neuropathy is usually not the initial complaint associated with acute arsenic poisoning. Arsenic-induced polyneuropathy has traditionally been described as an axonal-loss sensorimotor polyneuropathy (low-amplitude/unelicitable sensory and motor conduction responses, often with preserved motor conduction velocities). The first symptoms of neuropathy have been reported to appear 1 to 3 weeks after the presumptive arsenic exposure [12,13]. Clinical involvement spans the spectrum from mild paresthesia with preserved ambulation to distal weakness, quadriplegia, and respiratory muscle insufficiency. Arsenic neuropathy is a symmetrical sensorimotor neuropathy, with the sensory component being more prominent in a "stocking-and-glove" distribution [13,14]. This polyneuropathy may progress in an ascending fashion to involve proximal arms and legs. Dysesthesias begin in the lower extremities, with severe painful burning sensation occurring in the soles of the feet. There is loss of vibration and positional sense, followed by the loss of pinprick, light touch, and temperature sensation. Motor dysfunction is characterized by the loss of deep tendon reflexes and muscle weakness. In severe poisoning, ascending weakness and paralysis may occur and involve the respiratory muscles, resulting in neuromuscular respiratory failure [15,16]. It has been reported that many of the patients with arsenic neuropathy were initially thought to have Landry–Guillain–Barré disease [12,16].

Because the fundamental lesion in arsenic toxicity is the loss of capillary integrity, increased glomerular capillary permeability may result in proteinuria. However, the kidneys are relatively spared from the direct toxic effects of arsenic. Hypovolemic shock associated with the prominent GI symptoms may lead to hypoperfusion of the kidneys, resulting in oliguria, acute tubular necrosis, and renal insufficiency or failure. The kidneys are the main route of excretion for arsenic compounds. Normal-functioning kidneys can excrete more than 100 mg of arsenic in the first 24 hours [17]. Because of shock and decreased glomerular filtration rate and depending on the dose of arsenic ingested, peak urinary arsenic excretion may often be delayed by 2 to 3 days. Hemodialysis contributes minimally to arsenic clearance compared with the normal-functioning kidneys [18].

Dermal changes occurring most frequently in arsenic-exposed humans are hyperpigmentation, hyperkeratosis, and skin cancer [19]. The lesions usually appear 1 to 6 weeks after the onset of the illness. In most cases, a diffuse, branny desquamation develops over the trunk and extremities; it is dry, scaling, and nonpruritic. Patchy hyperpigmentation—dark-brown patches with scattered pale spots, sometimes described as "raindrops on a dusty road"—occurs particularly on the eyelids, temples, axillae, neck, nipples, and groin. Arsenic hyperkeratosis usually appears as cornlike elevations, less than 1 cm in diameter, occurring most frequently on the palms of the hands and on the soles of the feet. Most cases of arsenic keratoses remain morphologically benign for decades, and in other cases, marked atypia (precancerous) develops and appears indistinguishable from Bowen's disease—an in situ squamous cell carcinoma. Skin lesions take several years to manifest the characteristic pigmented changes and hyperkeratoses, whereas it takes up to 40 years before skin cancer becomes evident. Brittle nails with transverse white bands (leukonychia striata arsenicalis transversus) appearing on the nails have been associated with arsenic poisoning and are known as Reynolds–Aldrich–Mees lines [20–22]. It reflects transient disruption of nail plate growth during acute poisoning. Leukonychia striata arsenicalis transversus takes about 5 to 6 weeks to appear over the lunulae after an acute poisoning. Thinning of the hair and patchy or diffuse alopecia are also associated with arsenic poisoning [12,23].

Diagnostic Evaluation

The temporal sequence of organ system injury may suggest acute arsenic intoxication. After a delay of minutes to hours, severe hemorrhagic gastroenteritis becomes evident, which may be accompanied by cardiovascular collapse or death. Bone marrow depression with leukopenia may appear within 4 days of arsenic ingestion and usually reaches a nadir at 1 to 2 weeks. Encephalopathy, congestive cardiomyopathy, noncardiogenic pulmonary edema, and cardiac conduction abnormalities may occur several days after improvement from the initial GI manifestation. Sensorimotor peripheral neuropathy may become apparent several weeks after resolution of the initial signs (gastroenteritis or shock) of intoxication resulting from ingestion.

The differentiation between arsenic neuropathy and Landry–Guillain–Barré disease is based on clinical and laboratory findings in that arsenic neuropathy rarely involves the cranial nerves, sensory manifestations are more prominent, weakness in the distal portions of the extremities is more severe, and the cerebrospinal fluid protein concentrations are usually less than 100 mg per dL [12,13].

Laboratory investigation should include complete blood count with peripheral smear, electrolytes, liver enzymes, creatine phosphokinase, arterial blood gas, renal profile with urine analysis, ECG, chest radiograph, and blood and urine arsenic concentrations. Nerve conduction velocity studies may be indicated if peripheral neurologic symptoms are present. Some arsenic compounds, particularly those of low solubility, are radiopaque, and if ingested, they may be visible on an abdominal radiograph.

The most important diagnostic test is urinary arsenic measurement. Urine arsenic concentrations may be measured as "spot," that is, the concentration in a single-voided urine specimen, reported in µg per L. Urine arsenic concentrations may also be measured as a timed urine collection, or the concentration in urine collected during a 12- to 24-hour period, reported in micrograms per 12 or 24 hours. The quantitative 24-hour urine collection is considered the most reliable. In an emergency situation, the spot urine sample may be of value. Normal total urinary arsenic values are less than 50 µg per L or less than 25 µg per 24 hours. In the first 2 to 3 days following acute symptomatic intoxications, total 24-hour urinary arsenic excretion is typically in excess of several thousand micrograms, with spot urine concentration greater than 1,000 µg per L, and depending on the severity, it may not return to background for weeks. Recent ingestion of seafood may markedly elevate urinary arsenic values for the next 2 days. Therefore, it is important to take a careful dietary history of the past 48 hours when only total urinary arsenic is measured. Speciation of the urinary arsenic can be performed in some laboratories. Otherwise, the urinary arsenic test should be repeated in 2 to 3 days. Whole blood arsenic, normally less than 1 µg per dL, may be elevated early on in acute intoxication. However, blood concentrations decline rapidly to normal values despite elevated urinary arsenic excretion and continuing symptoms. Elevated arsenic content in hair and nail segments, normally less than 1 part per million, may persist for months after urinary arsenic values have returned to background. However, caution should be exercised when interpreting the arsenic content obtained from hair and nails because the arsenic content of these specimens may be increased by external exposure.

Management

The management of acute arsenic poisoning relies on supportive care and chelation therapy. Treatment begins with eliminating further exposure to the toxin and providing basic and advanced life support. Anyone with arsenic intoxication necessitating hospitalization should initially be admitted to an intensive care unit (ICU).

Gastric lavage should be performed following an acute ingestion and should be considered if the ingestion has been within the past 24 hours, as some arsenic compounds of low solubility may be retained in the stomach for a prolonged period of time. Frequently, seriously poisoned patients will have already vomited, evacuating some of their stomach contents. Activated charcoal and cathartics may be used, but their efficacy is unclear [24]. When there is evidence of a heavy metal burden on an abdominal radiograph, whole-bowel irrigation (WBI) with a polyethylene glycol electrolyte solution may rapidly help clear the GI tract of the metallic load. However, the absence of radiopacities on the abdominal radiograph is nondiagnostic and WBI should still be considered when there is a definite history that a poorly soluble arsenic compound has been ingested.

Intravascular volume depletion may require aggressive replacement with crystalloids, colloids, and blood products. Vasopressors are recommended for refractory hypotension. Invasive monitoring of the patient's hemodynamic status may be necessary.

In acute arsenic poisoning, extended cardiac monitoring for ventricular dysrhythmias is indicated for all patients who have prolonged QTc on their ECG. Electrolyte abnormalities—in particular, hypokalemia and hypomagnesemia—should be aggressively corrected, and concomitant QTc interval–prolonging drugs should be avoided. Serum potassium concentrations should be maintained at more than 4.0 mmol per L and magnesium concentrations at more than 1.8 mg per dL (0.74 mmol per L). There are no good data to indicate that suppression of ventricular dysrhythmias decreases mortality rates. If dysrhythmias occur, they should be treated according to current advanced cardiac life support guidelines. Type IA antidysrhythmic cardiac medications should be avoided because these drugs may themselves cause further QTc prolongation and worsen the polymorphic ventricular tachycardia. Lidocaine, magnesium, and isoproterenol have been used with limited success in the management of arsenic-induced torsades de pointes. A transvenous pacemaker for overdrive pacing may be necessary. Noncardiogenic and cardiogenic pulmonary edema should be managed according to current guidelines. In patients receiving arsenic trioxide induction therapy who develop prolonged QTc of more than 500 milliseconds on ECG, the risk/benefits of continuing therapy should be considered.

Hematologic effects of arsenic poisoning should be managed symptomatically with blood product transfusions and antibiotics as necessary for severe anemia, bleeding, or infections.

Patients with arsenic polyneuropathy should be given analgesics for pain and physical therapy for rehabilitation. Patients with polyneuropathy associated with severe arsenic poisoning should be observed closely for respiratory dysfunction. Neuromuscular respiratory failure may be delayed 1 to 2 months after the initial presentation. In cases in which there is progressive sensorimotor dysfunction, particularly ascending weakness, respiratory muscle function should be monitored carefully. When there is evidence of impending neuromuscular respiratory failure, aggressive supportive measures should be initiated in a timely fashion.

Patients with renal failure may benefit from hemodialysis. However, hemodialysis has limited use when normal renal function is present. Hemodialysis (initiated 24 to 96 hours postingestion) has been reported to remove about 4 mg of arsenic during a 4-hour period in patients with established renal failure [18]. It should not be surprising that only small amounts of arsenic are removed by dialysis as minimal amounts of arsenic are left in the central compartment once tissue distribution and equilibration is complete.

The principle behind chelation therapy is to increase excretion of the metal and decrease the target organ's metal burden. A chelator is an organic compound that has a selective affinity for heavy metals. It competes with tissues and other compounds containing thiol groups for metal ions, removes metal ions that previously have been bound, and binds with the metal ion to form a stable complex (chelate), rendering the metal less reactive and less toxic. The metal–chelator complex is water soluble and can be excreted in the urine, bile, or both, and to some extent, it can be removed by hemodialysis.

Dimercaprol (2,3-dimercapto-1-propanol [British anti-Lewisite, BAL]) is the traditional chelating agent that has been used clinically in arsenic poisoning. In humans and animal models, the antidotal efficacy of BAL has been shown to be most effective when it was promptly administered (i.e., minutes to hours) after acute arsenic exposure [25]. In cases of suspected acute symptomatic intoxication, treatment should not be delayed while waiting for specific laboratory confirmation. BAL is administered parenterally as a deep intramuscular (IM) injection. The initial dose is 3 to 5 mg per kg every 4 hours, gradually tapering to every 12 hours during the next several days. As the patient improves, this may be switched to 2,3-dimercaptosuccinic acid (DMSA; succimer) (see section "Lead" of this chapter). In the United States, DMSA is available only in an oral formulation. This precludes its use in acute severe arsenic intoxication when shock, vomiting, gastroenteritis, and splanchnic edema limit GI absorption. For patients with stable GI and cardiovascular status, a dose regimen of 10 mg per kg every 8 hours for 5 days, reduced to every 12 hours for another 2 weeks, may be employed. d-Penicillamine has also been reported to be successful adjunct treatment in cases of acute pediatric arsenic toxicity [26]. Oral d-penicillamine, 25 mg per kg every 6 hours (maximum of 1 g per day), should be used if BAL or DMSA is unavailable or if the patient is unable to tolerate these medications. Disadvantages in using d-penicillamine include that it is administered only by the oral route, it is usually not well tolerated, it should be used with caution in patients who are allergic to penicillin, and it entails potential enhanced absorption of arsenic–chelate complex. Adverse drug events associated with long-term d-penicillamine treatment include fever, pruritus, leukopenia, thrombocytopenia, eosinophilia, and renal toxicity. A complete blood count and renal function tests should be monitored weekly during d-penicillamine therapy.

BAL and its metal chelate dissociate in an acid medium and maintenance of an alkaline urine may protect the kidneys during chelation therapy [27]. BAL should be administered with caution in patients with glucose-6-phosphate dehydrogenase deficiency because it may cause hemolysis. The adverse drug events of BAL appear to be dose dependent, with an incidence of greater than 50% at a dose of 5 mg per kg [28]. The reported adverse drug events include pain at the injection site; systolic and diastolic hypertension with tachycardia; nausea; vomiting; headache; burning or constricting sensation in the mouth, throat, and eyes; lacrimation; salivation; rhinorrhea; muscle aches; tingling of the extremities; pain in the teeth; sense of constriction in the chest; abdominal pain; sterile or pyogenic abscesses at the site of injection; and a feeling of anxiety or unrest. In addition to these adverse drug events, a febrile reaction may occur in children. These signs and symptoms are most severe within 30 minutes after administration of BAL and usually dissipate within 1 to 1.5 hours. The adverse drug events may be lessened by the use of epinephrine or by pretreatment with antihistamine or ephedrine [28].

The therapeutic end points of chelation are poorly defined. Usually 24-hour urinary arsenic excretion is followed before, during, and after chelation with continued chelation therapy until the urinary arsenic excretion is less than 25 µg per 24 hours. Alternatively, when it can be demonstrated that more than 90% of the total arsenic excreted in the urine is in the form of MMA and DMA, endogenous biomethylation and detoxification may obviate the need for continued chelation [5]. This is likely to occur during the recovery period when urinary inorganic arsenic concentration has declined to less than 100 µg per 24 hours or total blood arsenic concentration is less than 200 µg per L [5].

Chelation therapy may not reverse neuropathy [12–14,29]. Early treatment may prevent incipient peripheral neuropathy in some, but not all, patients. However, the value of chelation in the treatment of an established arsenic neuropathy has not been demonstrated. In cases of chronic symptomatic arsenic intoxication with high urinary arsenic excretion, an empiric course of chelation may be warranted.

ARSINE GAS

Arsine (AsH_3) is a colorless, nonirritating, inflammable gas with a garlicky odor. It is considered to be the most toxic of the arsenic compounds. The garlic-like odor is not a reliable indicator of exposure as hazardous effects may occur below the odor threshold [30]. Exposure usually occurs in industrial/occupational settings, such as smelting and refining of metals and ores, galvanizing, soldering, etching, lead plating, metallurgy, burning fossil fuels, and the microelectronic/semiconductor industry [31]. (Computer chips made of gallium arsenide are etched with strong acids.)

Pharmacology

Arsine binds to red blood cells (RBCs) causing a rapid and severe Coombs' negative hemolytic anemia. The exact mechanism by which arsine is lytic to the RBC has not been definitively elucidated [31,32]. In vitro and animal studies indicate that hemolysis requires the presence of oxygen, there is a reduction in the RBCs' glutathione concentration, which is time- and concentration dependent on arsine gas exposure, and there is an inverse correlation between the reduced glutathione concentration and the extent of hemolysis. These findings are consistent with a mechanism of oxidative stress-induced damages to the RBCs, resulting in hemolysis.

Toxic concentrations of arsine appear to have deleterious effect on the kidneys. Acute renal failure was often a common cause of death prior to advent of hemodialysis [31,33,34]. Postulated mechanisms of arsine-induced renal failure include direct toxic effects of arsine on renal tubular cell respiration, hypoxia due to the hemolytic anemia, and the massive release of the "arsenic–hemoglobin–haptoglobin complex" precipitating in the tubular lumen, resulting in a toxic effect on the nephron [35]. Depending on the severity, renal failure may be evident by 72 hours from the time of exposure [31].

Clinical Toxicity

The severity and time to manifestation of arsine poisoning depend on the concentration and duration of the exposure. After an acute massive exposure, death may occur without the classic signs and symptoms of arsine poisoning. It is believed that after low-concentration exposures, arsine is rapidly and efficiently cleared from plasma into the RBCs. However, high concentrations of arsine may exceed the binding capacity of the erythrocytes, and the gas may directly damage vital organs. In cases in which signs and symptoms of arsine poisoning develop over time, the associated morbidity and mortality is partly related to the consequences of its hematologic and renal effects. In general, after a significant exposure to arsine, there is usually

a delay of 2 to 24 hours before symptoms of arsine poisoning become apparent [31].

Initial complaints include dizziness, malaise, weakness, dyspnea, nausea, vomiting, diarrhea, headache, and abdominal pain [31,36]. Dark-red discoloration of the urine, hemoglobinuria, and/or hematuria frequently appear 4 to 12 hours after inhalation of arsine. Depending on the severity of the exposure, reddish staining of the conjunctiva and duskily bronzed skin may become apparent within 12 to 48 hours [36]. However, the sensitivity of this sign is unclear. The conjunctival and skin discoloration is due to the presence of hemoglobin. This should be distinguished from true jaundice due to the presence of bilirubin. The triad of abdominal pain, hematuria, and bronze-tinted skin is recognized as a characteristic clinical feature of arsine poisoning [31].

In one study, ECG changes associated with arsine poisoning included peaked T waves, particularly in the precordial leads [30]. The most pronounced T-wave changes occurred between the second and the twelfth day after exposure. The severity of illness did not correlate with the height of the T wave. There was no delay in atrioventricular or intraventricular conduction times. There was progressive normalization of the T-wave amplitude evident on the weekly follow-up ECG. The exact cause of the ECG change remains speculative.

Management

All patients hospitalized for arsine poisoning should be admitted in the ICU. The management of arsine poisoning should be directed at preventing further exposure to the gas, restoring the intravascular RBC concentration, monitoring the serum potassium, preventing further renal insult, and providing aggressive supportive care. In cases of acute and severe arsine poisoning, exchange transfusion or plasma exchange may be an efficient and effective means of management [31,34,37]. It is important to maintain good urine output (2 to 3 mL per kg per hour) at all times. Alkalinization of the urine has been recommended to prevent deposition of RBC breakdown products in the kidneys. In situations in which there is evidence of renal insufficiency or failure, both exchange transfusion and hemodialysis may be required. There are practical and theoretic considerations for using exchange transfusion. It restores the intravascular RBC concentration and removes erythrocyte debris and arsenic–hemoglobin complexes [34]. Hemolysis due to arsine poisoning can be a dynamic process; there is one report of ongoing hemolysis for at least 4 days in patients not selected for exchange transfusion [38]. Theoretic support for the use of exchange transfusion came from animal studies where a large proportion of the fixed arsenic in the blood of animals poisoned with arsine was in a nondialyzable form, and adequate removal of arsine and its associated toxic complexes would be a problem with hemodialysis alone. It has been suggested that with early diagnosis of arsine poisoning and prompt institution of exchange transfusion, the incidence of renal damage and long-term renal insufficiency may be reduced [33,38].

The results of using BAL in the treatment of acute arsine poisoning have been disappointing [36,39]. BAL does not appear to afford protection against arsine-induced hemolysis. It remains speculative whether BAL would be of benefit in subacute or chronic arsine poisoning [31].

LEAD

The use of lead and its environmental contamination has increased dramatically since the beginning of the Industrial Revolution. However, for the past 20 years, environmental and occupational exposure to lead as well as the severity of lead poisoning have decreased because of government regulations and increased public health awareness of the problems associated with lead, especially at low-concentration exposures.

The major environmental sources of lead include vehicle exhaust, paint, food, and water. Combustion of leaded gasoline by motor vehicles produced lead in automobile emissions, which is the main source of airborne lead. Airborne lead can be inhaled directly or deposited in the environment (soil, water, and crops). The content of lead in residential paint was not regulated until 1977. More than half of the older residential and commercial structures built prior to 1960 have been painted with lead-based paints. With time, flaking, chipping, peeling, and chalking of the paint occurs—a potential source of lead exposure. Industrial use of corrosion-resistant lead paint continues. High-concentration exposure may result from renovation, sandblasting, torching, or demolition of older applications. Food may contain lead that has been deposited in the soil or water. Food may be contaminated with lead when it is harvested, transported, processed, packaged, and prepared. Lead exposure may occur from use of lead-glazed pottery or ceramic ware for cooking and eating as well as from the consumption of food from lead-soldered cans. Water from leaded pipes, soldered plumbing, and water coolers is also a potential source of lead exposure. Some traditional Hispanic, Asian, and Middle Eastern folk medicine has been shown to contain significant amounts of lead. Mexican folk remedies, "azarcon" and "greta," are prescribed by the local folk healers (curanderos) to treat nonspecific GI symptoms collectively known as "empacho." Azarcon is a bright-orange powder and greta is a fine yellowish powder. Other names such as alarcon, coral, liga, Maria Luisa, and rueda have been given to these lead-containing folk remedies. In Asian communities, lead-containing folk remedies include bali goli, chuifong tokuwan, ghasard, knadu, payloo-ah, and Po Ying Tan. Middle Eastern lead-containing folk medicines include alkohl, cebagin, kohl, saoott, and surma.

The most significant way in which children are exposed to lead is through inhalation and ingestion. Children can ingest chips from lead-painted surfaces, or by mouthing items contaminated with lead from dust, soil, or paint. Some children are given folk remedies containing large quantities of lead. Another potential source of lead exposure in children is the preparation of infant formulas in vessels with lead solder.

Aside from the environmental sources, lead exposure in adults primarily comes from the occupational setting, particularly for electricians; cable splicers; plumbers; lead, copper, zinc, and silver miners; printers; lead smelters and refiners; steel welders and cutters; painters; auto repairers (radiator repair mechanics); sandblasting, demolition, and construction workers; battery manufacturers; solderers; bricklayers; silversmiths; glass manufacturers; and ship builders. One source of lead exposure that is not often considered is retained lead bullets, especially those that are near synovial surfaces.

Hobbies and related activities such as home remodeling, target shooting at indoor firing ranges, stained glass making, glazed pottery making, lead soldering, and making illicitly distilled whiskey ("moonshine") can potentially subject adults and their families to high concentrations of lead.

Pharmacology

In adults, about 10% of an ingested dose is absorbed, whereas in children, up to 50% may be absorbed. GI absorption may be increased by iron or calcium deficiency and varies directly with the solubility of the lead compound ingested and inversely with particle size. The oral dose associated with the lowest observable effect level in humans is uncertain. Acute human ingestion of 15 g of lead oxide has resulted in fatality.

Inhalation of lead is a significant route of exposure as lead particles (e.g., dust) and fumes can potentially reach the alveoli, where absorption from the lower respiratory tract is nearly complete. Airborne lead particles are usually too large to enter the alveoli of small children. These particles (when inhaled) are returned to the posterior pharynx through ciliary action and swallowed. Dermal absorption of lead is rapid and extensive for alkyl lead compounds, but minimal for inorganic lead.

After absorption, almost all lead in the blood is located within the RBCs [40]. RBC lead has a half-life of 30 to 40 days and is circulated and distributed into soft tissues and bones. The half-life of lead in the soft tissues is about 40 days, whereas the half-life in bones is 20 to 30 years. Hence, blood lead concentration may be declining as the soft tissue and bone burdens are rising. Equilibration between bone and blood lead does occur. The major depot for lead in the body is the skeletal system, which contains more than 90% in adults and more than 70% in children, in terms of the total body lead burden [41]. The primary sources of lead that cause clinical and subclinical symptoms are the blood and soft tissues. Lead that is deposited and incorporated into the matrix of bone can be mobilized during pregnancy, lactation, osteoporosis, and prolonged immobilization [42]. In addition, lead that is deposited in bone may have some toxic effects on bone growth and function.

The kidneys filter lead unchanged (with some active tubular transport at high concentrations), and the excretion rate depends on the glomerular filtration rate and renal blood flow. The kidneys account for about 75% of daily lead loss [40]. However, elimination of lead from the body is influenced by the relative concentration of lead in the various body compartments.

Common forms of inorganic lead are generally devoid of significant irritant or corrosive effects. However, alkyl lead compounds may be moderately irritating. The multisystemic toxicity of lead is mediated by at least two primary mechanisms: the inhibition of enzymatic processes, sometimes as a result of sulfhydryl group binding, and interaction with essential cations, in particular calcium, zinc, and ferrous iron. Pathologic alterations in cellular and mitochondrial membranes, neurotransmitter biosynthesis and function, heme biosynthesis, and nucleotide metabolism may also occur.

One of the principal toxic effects of lead is inhibition of enzymes along the heme biosynthesis pathway. Specifically, lead inhibits the enzymes δ-aminolevulinic acid (ALA) dehydrase and ferrochelatase. As a result, δ-ALA cannot be converted to porphobilinogen and iron cannot be incorporated into protoporphyrin IX. This is reflected by a measurable increase in serum ALA and protoporphyrin concentrations. The increase in protoporphyrin forms the basis of the erythrocyte protoporphyrin (EP) test, which has been used to screen for chronic lead exposure. Lead also inhibits the nonenzymatic mobilization of iron stores, which further contributes to the effect of anemia. Impaired heme biosynthesis may have widespread effects because of its impact on the cytochrome systems. In addition, lead appears to shorten erythrocyte survival time by interfering with the sodium-potassium–adenosine triphosphatase pump mechanism and by attaching to RBC membranes, causing increased mechanical fragility and cell lysis. Decreased heme synthesis and increased RBC destruction results in reticulocytosis. Inhibition of pyrimidine-5′-nucleotidase by lead results in accumulation of ribonucleic acid degradation products and aggregation of ribosomes in RBCs, which produce punctate basophilic stippling. However, neither anemia nor basophilic stippling is a sensitive or specific indicator of lead intoxication. Lead-induced anemia results from either a prolonged exposure or a concentrated short-term exposure with a latent period of several weeks.

Lead toxicity produces anatomic lesions in the proximal tubule and loops of Henle, which is characterized by round acidophilic intranuclear inclusion bodies. Most often, lead-induced renal injury is associated with prolonged exposure to large amounts of lead, resulting in progressive renal insufficiency.

The toxic effects of lead involve both the peripheral nervous system and the central nervous system (CNS). Peripheral nervous system toxicity is known as lead palsy and is due to the degenerative changes in the motoneurons and their axons, with secondary effects involving the myelin sheaths [43]. Lead palsy is usually a pure motor neuropathy and is the result of advanced chronic lead poisoning. Both adults and children can present with CNS dysfunction; however, children are the ones who present with encephalopathy [44,45]. Although lead encephalopathy is rare today, it is the most serious consequence of lead poisoning and is probably due to inhibition of the intracellular enzyme systems within the CNS.

Clinical Toxicity

Poisoning is usually the result of continued exposure to small amounts of lead rather than a single acute event. However, acute ingestion can produce lead toxicity [44, 46]. Usually the clinical presentation of acute lead toxicity appears to be associated with a sharp incremental rise in the concentration of lead in various soft tissues, and this often occurs against the background of chronic lead poisoning.

The multisystemic toxicity of lead presents a spectrum of clinical findings ranging from overt, life-threatening intoxication to subtle, subclinical deficits. Acute ingestion of very large quantities of lead (gram quantities) may cause abdominal pain, toxic hepatitis, and anemia (usually hemolytic).

Subacute or chronic exposure causes nonspecific constitutional symptoms such as fatigue, arthralgias, decreased libido, irritability, impotence, depression, anorexia, malaise, myalgias, weight loss, and insomnia [47]. GI symptoms include nausea, constipation or diarrhea, and intestinal spasm. The intestinal spasm, "lead colic," can cause severe, excruciating, paroxysmal, abdominal pain. CNS findings range from impaired concentration, visual–motor coordination, and headache, to severe, life-threatening encephalopathy characterized by vomiting, tremors, hyperirritability, ataxia, confusion, delirium, lethargy, obtundation, convulsions, coma, and death. A peripheral motor neuropathy, predominantly affecting the upper extremities, may result in extensor weakness. In rare instances, severe cases may produce frank "wrist drop." Decreased intelligence, impaired neurobehavioral development, decreased stature or growth, and diminished auditory acuity may occur. Hematologic manifestations include normochromic or microcytic anemia. This may be accompanied by basophilic stippling of the erythrocytes. Nephrotoxic effects include overt reversible acute tubular dysfunction, in particular, Fanconi-like aminoaciduria in children, and chronic progressive renal interstitial fibrosis following heavy long-term exposure in lead workers. Sometimes hyperuricemia, with or without evidence of gout, may be associated with the renal insufficiency [48]. An association between lead exposure and hypertension may exist in susceptible populations.

Repeated, intentional inhalation of leaded gasoline may result in ataxia, myoclonic jerking, hyperreflexia, delirium, and seizures.

Diagnostic Evaluation

Although encephalopathy and abdominal colic following a suspect activity may readily suggest the diagnosis of severe lead intoxication, the nonspecific nature of mild-to-moderate intoxication frequently presents a diagnostic challenge.

Exposure is often not suspected, and symptoms are commonly attributed to a "nonspecific viral illness." Lead intoxication should be considered in patients presenting with multisystem findings including headache, abdominal pain, and anemia, and less commonly, motor neuropathy, gout, and renal insufficiency. Lead encephalopathy should be considered in any child with delirium or seizures, and milder degrees of intoxication should be considered in children with neurobehavioral deficits or developmental delays. Lead encephalopathy has usually been associated with blood lead concentrations of 100 µg per dL or more [49]. Blood lead concentrations greater than 80 µg per dL are occasionally associated with acute severe illness.

Whole blood lead concentration and EP are the two methods most commonly used in testing for lead intoxication. Whole blood lead concentration is the most useful screening and diagnostic test for acute or recent lead exposure. This test does not measure total body lead burden, but it does reflect abrupt changes in lead exposure. Elevation in EP (> 35 µg per dL) reflects lead-induced inhibition of heme biosynthesis. Because only actively forming erythrocytes are affected, elevations in EP will typically lag behind lead exposure by 2 to 6 weeks. EP value may help distinguish between recent and remote lead exposure. An extremely high whole blood lead concentration in the presence of a normal EP concentration would suggest a recent lead exposure. An elevated EP concentration is not specific for lead exposure, and may also occur with iron deficiency. EP is not a sensitive screening tool for low-concentration (< 30 µg per dL) lead poisoning. EP and blood lead concentrations should be used as complementary methods of testing for lead intoxication.

EP, free EP, and zinc EP measure the same basic process and have very similar interpretations, but are not identical. EP is the most precise terminology. Because lead blocks (ferrochelatase) the final step in heme biosynthesis, it was originally thought that "free" EP was formed. However, it was subsequently shown that other porphyrins were measured in minute amounts, and most protoporphyrin had nonenzymatically bound zinc and was therefore not "free" [50].

Relationships between blood lead concentrations and clinical findings have generally been based on subacute and chronic exposure, and not on transiently high values that may result immediately following exposure prior to tissue equilibration (Table 133.2). Interindividual variability in response is extensive.

Measurement of urinary lead excretion is not very useful in the diagnosis of lead exposure. Urinary lead excretion reflects the plasma lead concentration, which increases and decreases more rapidly than blood lead concentration.

Nonspecific laboratory criteria consistent with lead toxicity include normochromic or microcytic anemia, basophilic stippling of RBC on peripheral smear, increased urinary ALA, and coproporphyrin. Liver transaminases may be elevated in acute intoxication. Low-molecular-weight proteinuria and enzymuria may precede elevations in serum creatinine. Radiopacities on abdominal radiograph may be evidence of lead in the GI tract following recent ingestion. This is especially true for lead-based ceramic glazes [46].

Management

Acute lead encephalopathy is a medical emergency that requires intensive care and monitoring of the patient. Prompt consultation with a toxicologist should be obtained to assist in the management. Because up to 25% of the children who survive an acute episode of encephalopathy sustain permanent CNS damage [49], medical treatment should be instituted before its onset. It has long been recommended that any child who is symptomatic from lead poisoning or has a whole blood lead concentration greater than 80 µg per dL should be hospitalized immediately and treated as a medical emergency [49]. More recently, the Centers for Disease Control has issued a statement that children with blood lead concentrations of 70 µg per dL or greater require immediate chelation therapy [51].

Although present-day recommendations for the treatment of lead encephalopathy were derived from experiences in managing children [49,52–54], they have been extrapolated to adults. The basic treatment plan consists of supportive measures and the use of chelating agents. As with any potential life-threatening emergency, assessment and aggressive management of the airway, breathing, and circulation should be paramount.

GI decontamination, beginning with gastric lavage, is indicated following acute ingestion of virtually any lead-containing substances because even small quantities of paint chip or a sip of lead-containing glaze may contain several hundred milligrams of lead. The use of activated charcoal has been suggested; however, its efficacy is unknown. Abdominal radiograph may reveal radiopaque foreign bodies in the GI tract following recent ingestion of lead-containing substances such as paint chips, lead weights, and lead-based ceramic glazes [46]. WBI with polyethylene glycol solution has been suggested as a means of decontaminating the GI tract when the presence of lead is evident on radiographic examination of the abdomen [46]. The effectiveness of WBI can be followed by serial abdominal radiographs. Although it is important to eliminate the source of continued lead absorption, therapy should not be delayed by attempts at GI decontamination, especially in cases

TABLE 133.2

WHOLE BLOOD LEAD CONCENTRATION AND ASSOCIATED CLINICAL FINDINGS

Whole blood lead concentration (µg/dL)	Associated clinical findings
< 25	Decreased intelligence and impaired neurobehavioral development among children with in utero or early childhood exposure; generally without demonstrable toxic effects in adults
20–60	Mild overt effects such as headache, irritability, difficulty concentrating, slowed reaction time, and impaired visual–motor coordination, and insomnia may emerge
	Anemia may begin to appear
	Reversible, subclinical slowing of motor nerve conduction velocity may be detected
60–80	Subclinical effects on renal function
	GI symptoms (e.g., anorexia, constipation, and/or diarrhea, and abdominal colic) may emerge
> 80	Serious overt intoxication, including abdominal pain (colic), and nephropathy
> 100	Encephalopathy and overt neuropathy

of encephalopathy. Ultimately, the chief priority is to identify and eradicate the source of lead exposure and institute control measures to prevent repeated intoxication. In addition, other possibly exposed persons should be promptly evaluated.

Lead-containing buckshot, shrapnel, or bullets in or adjacent to synovial spaces should be surgically removed if possible, especially if associated with evidence of systemic lead absorption.

In a child presenting with encephalopathy, immediate treatment should begin with establishing an adequate urine output [49]. This can be accomplished by intravenous (IV) infusion (10 to 20 mL per kg) of 10% dextrose in water during 1 to 2 hours. If this fails to produce a urine output, infusion of a 20% mannitol solution (1 to 2 g per kg) is recommended at 1 mL per minute. Once urine output has been established, IV fluids should be restricted to the calculated basal water and electrolyte requirements plus a careful assessment of continuing losses. An indwelling Foley catheter should be used to monitor the rate of urine formation. IV fluids should be adjusted hourly in order to maintain urine flow that is within the basal metabolic limits, which is 0.35 to 0.50 mL of urine secreted per calorie metabolized per 24 hours or 350 to 500 mL per m^2 per 24 hours. Such management is designed to avoid excessive fluid administration and prevent further development of cerebral edema. Severe lead encephalopathy can occur without cerebral edema [52]. However, when cerebral edema occurs in the presence of encephalopathy, there is further insult to the brain, and it may be the immediate cause of death. Children with encephalopathy may exhibit syndrome of inappropriate antidiuretic hormone [54].

Benzodiazepines should be used for immediate control of seizures. If paralysis with sedation or general anesthesia is required for controlling seizure activities, a bedside electroencephalogram should be obtained to rule out electrical status. Because high doses of phenytoin and phenobarbital were required to control the initial seizures in lead encephalopathy, paraldehyde was formerly used [54]. However, barbiturates were recommended in the prevention of seizures during the early convalescent phase of lead encephalopathy [49]. Repeated seizures and hypoxia can exacerbate cerebral edema [49,54], so it was suggested that anticonvulsants be administered when there is evidence of increased muscle tone or muscle twitching; one should not wait for obvious seizure activity [49].

Computed tomography scan of the head should be performed in patients presenting with encephalopathy to rule out cerebral edema. If there is evidence of cerebral edema, intracranial pressure (ICP) monitoring should be performed (with neurosurgical consultation) to assist with the management of the patient. Avoid performing a lumbar puncture when there is increased ICP associated with cerebral edema. Measures advocated to control cerebral edema and increased ICP include careful sedation and neuromuscular paralysis, elevation of the head of the bed, hyperventilation, restriction of fluid therapy, ventricular drainage, diuretics (e.g., mannitol or furosemide), and steroids. These measures are "borrowed" from the neurosurgical experience in managing increased ICP. Restriction of fluids and the use of mannitol have been discussed previously. Maintaining the arterial partial pressure of carbon dioxide between 25 and 30 mm Hg by controlled hyperventilation has been shown to result in cerebral vasoconstriction and reduced ICP. The benefit of glucocorticoids in treating perifocal vasogenic edema due to an intrinsic intracranial mass lesion is well established. However, glucocorticoids have not been proved beneficial in models of intracellular cytotoxic edema, and neurologic outcome studies do not support the routine use of glucocorticoids following head injury, global brain ischemia, and cerebral vascular accidents [55]. If the cerebral edema associated with lead encephalopathy is believed to be vasogenic in origin, the empiric use of dexamethasone should be considered. Surgical attempts to relieve ICP by flap craniotomy have not been shown to be beneficial [56]. However, ventricular drainage (via the intracranial bolt placed for ICP monitoring) may effectively reduce a rising ICP.

Chelating agents have been shown to decrease blood lead concentrations and increase urinary lead excretion. Chelation has also been associated with improvement in symptoms and decreased mortality. However, controlled clinical trials demonstrating therapeutic efficacy is lacking, and treatment recommendations have been largely empiric. Although there appears to have been a sharp reduction in pediatric mortality due to acute lead encephalopathy with the advent of chelation treatment, there were concomitant advances in the management of elevated ICP, and the decline in mortality cannot necessarily be attributed to the use of chelation alone. BAL and calcium disodium edetate (CaEDTA) are the two chelators used in the treatment of lead encephalopathy. DMSA is used for less severe poisoning.

BAL increases both fecal and urinary excretion of lead. It is distributed widely throughout all body tissues, including the brain and RBCs. Because BAL is excreted in the urine and to some extent in the bile, patients with renal failure are not precluded from the use of BAL, whereas patients with hepatic insufficiency may have a lower tolerance to BAL [57]. Details regarding the use of this agent are discussed in section "Arsenic" of this chapter. BAL and medicinal iron can form a toxic complex that is a potent emetic, but the treatment of anemia with iron should be delayed until BAL therapy has been completed. If severe anemia requires prompt intervention during chelation therapy, transfusion would be preferable.

CaEDTA enhances the elimination of lead and, to a lesser extent, the elimination of endogenous metals (e.g., zinc, manganese, iron, and copper). Increased urinary lead excretion begins within 1 hour and is followed by a decrease in whole blood lead concentration over the course of treatment. CaEDTA diffuses rapidly and uniformly throughout the body, but it does not appear to enter RBCs and very slowly diffuses across the blood–brain barrier [58]. CaEDTA mobilizes lead (primarily) from soft tissues and from a fraction of the larger lead stores present in bone. CaEDTA is not metabolized; rather, it is cleared from the body by urinary excretion. It can be administered IV or IM, with the former being the preferred and most effective route. Oral administration of CaEDTA has been known to increase absorption of lead from the GI tract; therefore, it should not be given by this route. The principal toxic effect of CaEDTA is on the kidneys, which can result in renal tubular necrosis [59]. The renal toxicity is dose related and reversible. Because CaEDTA increases renal excretion of lead and its accumulation increases the risk of nephrotoxicity, anuria would be a contraindication in its use. An adequate urine flow should be established before initiating CaEDTA therapy.

In the management of patients with lead encephalopathy, some clinicians would advocate the use of BAL and CaEDTA beginning with a priming dose of BAL at the same time that an adequate urine output is being established. The priming dose of BAL is 75 mg per m^2 (3 to 5 mg per kg) IM and is administered every 4 hours. After 4 hours have elapsed since the priming dose of BAL, a continuous slow IV infusion of CaEDTA 1,500 mg per m^2 per day (30 mg per kg per day) is started. In cases where there is evidence of cerebral edema and/or increased ICP associated with encephalopathy, CaEDTA (same dosage) should be given by deep IM injection in two to three divided doses every 8 to 12 hours. When the IM route is preferred, procaine (0.5%) should be given along with CaEDTA because IM administration of CaEDTA is extremely painful. BAL and CaEDTA are usually continued for 5 days. In patients with high body lead burdens, cessation of chelation is often followed by a rebound in blood lead concentration as bone stores equilibrate with lower soft-tissue concentrations.

A second course of chelation may be considered on the basis of whole blood lead concentration after 2 days of interruption of BAL and CaEDTA treatment, and the persistence or recurrence of symptoms. A third course may be required if the whole blood concentration rebounds to 50 µg per dL or greater within 48 hours after the second chelation treatment. If chelation is required for the third time, it should begin a week after the last dose of BAL and CaEDTA.

In the management of symptomatic patients with lead poisoning who are not overtly encephalopathic, most clinicians would advocate the same course of treatment as for those with encephalopathy, but with lower doses of BAL and CaEDTA. The priming dose of BAL is 50 mg per m^2 (2 to 3 mg per kg) IM and is administered every 4 hours. After 4 hours have elapsed since the priming dose of BAL, a continuous slow IV infusion of CaEDTA 1,000 mg per m^2 per day (20 to 30 mg per kg per day) is started. Alternatively, CaEDTA may be given in two to three divided doses every 8 to 12 hours by continuous infusion or deep IM injection. BAL and CaEDTA should be continued for 5 days with daily monitoring of whole blood lead concentrations. BAL may be discontinued any time during these 5 days if the whole blood lead concentration decreases to less than 50 µg per dL, but CaEDTA treatment should continue for 5 days. A second or third course of chelation may be considered on the basis of the same guidelines as discussed in the previous paragraph.

In the management of asymptomatic patients with whole blood lead concentrations 70 g per dL or greater, some clinicians would advocate the use of BAL and CaEDTA in the same doses and with the same guidelines as for treatment of symptomatic lead poisoning without encephalopathy. A second course of chelation with CaEDTA alone may be necessary if the whole blood lead concentration rebounds to 50 µg per dL or more within 5 to 7 days after chelation has ceased. Some clinicians prefer DMSA.

A water-soluble analogue of BAL, DMSA enhances the urinary excretion of lead, mercury, and arsenic. It has an insignificant effect on elimination of the endogenous minerals calcium, iron, and magnesium. Minor increases in zinc and copper excretion may occur. Oral DMSA is rapidly but variably absorbed, with peak blood concentrations occurring between 1 and 2 hours. The drug is predominantly cleared by the kidneys, with peak urinary elimination of the parent drug and its metabolites occurring between 2 and 4 hours. DMSA is approved for use in lead and mercury intoxications, in which it is associated with increased urinary excretion of the metals, and concurrent reversal of metal-induced enzyme inhibition. Oral DMSA is comparable to parenteral CaEDTA in decreasing whole blood lead concentration during treatment. Although treatment with DMSA has been associated with subjective clinical improvement, controlled clinical trials demonstrating therapeutic efficacy have not been reported. Reported adverse drug events of DMSA include GI disturbances (anorexia, nausea, vomiting, and diarrhea), mercaptan-like (sulfur) odor to the urine, rashes, mild-to-moderate neutropenia, and mild, reversible increases in hepatic transaminases.

Although DMSA is officially approved for use only in children with whole blood concentration in excess of 45 µg per dL, it has similar ability to lower whole blood lead concentration in adults. Treatment is initiated at an oral dose of 10 mg per kg (350 mg per m^2) every 8 hours for 5 days. Treatment is then continued at the same dose every 12 hours for an additional 2 weeks. An additional course of treatment may be considered on the basis of posttreatment whole blood lead concentrations and the persistence or recurrence of symptoms. Whole blood lead concentration may decline by more than 50% during treatment, but patients with large body burdens may experience rebound to within 20% of pretreatment concentrations as bone body stores reequilibrate with tissue concentrations. An interval of 2 or more weeks may be indicated to assess the extent of posttreatment rebound in whole blood lead concentration. Experience with oral DMSA in severe lead intoxication (e.g., lead encephalopathy or lead colic) is very limited, and consideration should be given to parenteral chelation therapy in such cases.

MERCURY

Mercury (Hg) is a naturally occurring metal that is mined chiefly as mercuric sulfate (HgS) in cinnabar ore. It is converted into three primary forms, each with a distinct toxicology: elemental (Hg^0) mercury, inorganic (mercurous [Hg^{+1}] and mercuric [Hg^{2+}]) mercury salts, and organic (alkyl and phenyl) mercury. The pattern and severity of toxicity are highly dependent on the form of mercury and route of exposure, mostly because of different pharmacokinetic profiles.

Elemental Mercury

Elemental mercury is the only metal that exists in liquid form at standard temperature and pressure. As such, metallic mercury can evaporate slowly at room temperature or rapidly when heated, and can contribute to the partial pressure of the ambient air that is breathed. A small spill in an enclosed space (e.g., a bedroom) can also produce high concentrations of mercury in the air because of its high vapor pressure. Various instruments contain elemental mercury including thermometers, manometers, barometers, switches, pumps, and special surgical tubes (such as Miller-Abbott, Canter, and Kaslow). Dental amalgam is prepared with elemental mercury and contains approximately 50% elemental mercury by weight.

Personnel in occupational settings who are potentially exposed include chlor-alkali mercury cell operation workers, electroplaters, explosives manufacturers, laboratory personnel, pesticide/fungicide production and application workers, manufacturers of batteries or mercury vapor lamps, metallurgists, and miners and processors of cinnabar, gold, silver, copper, and zinc. Exposure to mercury vapor from elemental mercury spill, work hazard, home gold ore purification, accidental heating of metallic mercury, and vacuum cleanup of a mercury spill have also been reported [60].

Pharmacology

When ingested, elemental mercury is poorly absorbed (< 0.01%) from the healthy, intact, and normal-functioning GI tract. In contrast, inhaled mercury vapor is believed to cross the alveolar membranes rapidly because of its high diffusibility and high lipid solubility. About 75% of the inhaled dose is retained [61]. The absorbed elemental mercury vapor rapidly diffuses into the RBCs, where it undergoes oxidation to the mercuric ion and binds to ligands in the RBC. However, a certain amount of the dissolved vapor persists in the plasma to reach the blood–brain barrier, which it crosses readily [62]. Once in the brain tissue, the dissolved mercury vapor is oxidized to mercuric ion, trapping it within the CNS, where it is available for binding tissue ligands. Elemental mercury vapor is also easily transported across the placenta [63].

Elemental mercury vapor is eliminated from the body mainly as mercuric ion by urinary and fecal routes. Exhalation of mercury vapor and secretion of mercuric ions in saliva and sweat do occur and contribute to the elimination process. The rate of excretion is dose dependent. Elemental mercury follows a biphasic elimination rate, initially rapid and then slow, with a biologic half-life in humans of about 60 days.

Mercuric ion has an affinity to bind and react with sulfhydryl moieties of proteins, leading to nonspecific inhibition of enzyme systems and pathologic alteration of cellular membranes.

The pulmonary and central nervous systems bear the brunt of the insult in elemental mercury vapor poisoning. Damage to the respiratory system results from acute inhalation exposure to high concentrations of elemental mercury vapor, which acts as a direct airway irritant and a cellular poison [60,64]. Pulmonary toxicity is characterized by exudative alveolar and interstitial edema, erosive bronchitis and bronchiolitis with interstitial pneumonitis, and desquamation of the bronchial epithelium. The ensuing obstruction results in alveolar dilatation, interstitial emphysema, pneumatocele formation, pneumothorax, and mediastinal emphysema.

In the CNS, a cumulative toxic effect occurs as the inhaled elemental mercury vapor is oxidized to mercuric ion, leading to progressive CNS dysfunction. As would be expected, CNS toxicity is typically the result of chronic elemental mercury vapor exposure.

Clinical Toxicity

The ingestion of elemental mercury usually causes no adverse effects [65]. However, systemic absorption of mercury is possible in the presence of any bowel abnormality affecting mucosal integrity or impeding normal motility and transit. In addition, inflammatory bowel disease or enteric fistula allowing for prolonged elemental mercury exposure and the conversion of metallic mercury to an inorganic absorbable ion has been reported [66]. Elemental mercury that is retained in the appendix can result in local inflammation, perforation, and the consequent possibility of systemic mercury intoxication. Signs of appendiceal inflammation or systemic mercury absorption and toxicity should be appropriately monitored and treated. Prophylactic appendectomy in the absence of signs and symptoms of appendicitis should be avoided because of the risk of mercury extravasation through the surgical anastomosis and intra-abdominal suppurative complications [67].

Subcutaneous injection of elemental mercury may cause a local fibrous reaction, local abscess, granuloma formation, and systemic embolization, and systemic absorption with toxic manifestations has been reported [68,69].

IV injected elemental mercury has been reported to cause pulmonary and systemic mercury embolization, associated with an elevated blood mercury concentration, and sequelae may include tremor, lower extremity weakness, and reduced carbon monoxide diffusing capacity [68,70,71]. Mercury extravasation at the injection site can produce a severe local inflammatory reaction. Granuloma formation with fibrosis and inflammation with systemic mercury absorption has also been reported.

Acute intense inhalation of mercury vapor in a confined or poorly ventilated space may result in death. Initial symptoms usually occur within several hours following exposure and include fever, chills, headache, dyspnea, gingivostomatitis, nausea, vomiting, metallic taste in the mouth, paroxysmal cough, tachypnea, chest tightness, diarrhea, and abdominal cramps [64]. These symptoms may subside or, in severe cases, may progress to interstitial pneumonitis, bilateral infiltrates, atelectasis, noncardiogenic pulmonary edema, interstitial pulmonary fibrosis, and death [64]. In addition, complications such as subcutaneous emphysema, pneumomediastinum, and pneumothorax may occur. Children younger than 30 months seem to be particularly susceptible to such exposures [72].

Aspiration of elemental mercury may cause no acute respiratory symptoms, cough and mild dyspnea, acute pneumonitis, or progressive cough with copious amounts of frankly bloody sputum production, leading to respiratory compromise and death [73]. Most patients remain asymptomatic or recover without any significant sequelae. In two cases, systemic absorption of the aspirated elemental mercury was suggested by elevations in the 24-hour urinary mercury concentrations, but neither patient became symptomatic. Elemental mercury was consistently evident on chest radiographs obtained on follow-up examination, which varied from 1 month to 20 years. One case with postmortem findings from the lungs 22 years later included globules of elemental mercury surrounded by extensive fibrosis and granuloma formation. Subclinical changes in peripheral nerve function and renal function have been reported, but symptomatic neuropathy and nephropathy are rare.

Diagnostic Evaluation

Diagnosis depends on integration of characteristic findings with a history of known or potential exposure, and the presence of elevated whole blood mercury concentration and urinary mercury excretion. Abdominal radiographs may be used to document the extent of the GI contamination following elemental mercury ingestion. Radiographs of the injection site may help to define the extent of the infiltrated mercury. Chest radiograph and computed axial tomography scan may be useful in determining the location of systemic embolization.

Whole blood and urinary mercury concentrations are useful in confirming exposure. In most people without occupational exposure, whole blood mercury concentration is less than 2 µg per dL and "spot" or single-voided urine mercury concentration is less than 10 µg per L. A quantitative 24-hour urinary mercury excretion, usually less than 50 µg per 24 hours, is probably the most useful tool in diagnosing acute exposure (Table 133.3).

Management

Any patient requiring hospitalization because of acute elemental mercury inhalation or aspiration should be admitted to the ICU. As with any potential life-threatening emergency, assessment and aggressive management of the airway, breathing, and circulation should be paramount. Treatment is primarily supportive. Another priority is to identify and eradicate the source of elemental mercury exposure and to identify and evaluate other possibly exposed persons.

In cases in which elemental mercury ingestion has been documented, WBI with polyethylene glycol electrolyte solution or surgical removal may be necessary, depending on radiographic evidence of mercury retention, elevated blood urine mercury concentrations, and the patient's clinical status. Repeat abdominal radiographs may be used to document the effectiveness of WBI or to follow the progress of the ingested metallic mercury.

Aggressive local wound management of the injection site(s) should include prompt excision of all readily accessible

TABLE 133.3

ELEMENTAL MERCURY VAPOR EXPOSURE

Urine mercury concentration (µg/L)	Associated clinical findings
30–50	Subclinical neuropsychiatric effects
50–100	Early subclinical tremor
> 100	Overt neuropsychiatric disturbances
> 200	True tremors

subcutaneous areas in which metallic mercury is demonstrated, copious saline irrigation to remove metallic mercury droplets, and suction removal of the mercury [74]. Surgical excision of mercury granulomas has also been recommended [68]. Injection of dimercaprol BAL into the wound is not recommended as it may delay wound healing [75].

Patients acutely exposed to elemental mercury vapor should be monitored closely for respiratory symptoms. Chest radiographs, arterial blood gases, and pulmonary function should be followed in symptomatic patients. Oxygen and bronchodilators should be administered as needed. Progressive deterioration of respiratory function may require aggressive airway management with tracheal intubation, mechanical ventilation, and positive end-expiratory pressure. Early treatment with corticosteroids has been used in an attempt to reduce the complication of pulmonary fibrosis. However, neither corticosteroids nor prophylactic antibiotics have proved to be beneficial in the management of elemental mercury vapor-induced pulmonary complications.

Patients who have aspirated elemental mercury should be managed in a similar fashion. Vigorous suctioning, postural drainage, and good pulmonary toilet may assist the patient in expectorating some of the aspirated mercury. In addition, bronchoscopy may be indicated.

Chelating agents that are commercially available in the United States for use in the treatment of mercury poisoning include BAL, DMSA, and d-penicillamine (see sections "Arsenic" and "Lead" of this chapter). The choice of chelator depends on the form of mercury involved and the presenting signs and symptoms of the patient. DMSA and d-penicillamine may facilitate the absorption of mercury from the GI tract and should not be given when there is still evidence of mercury present in the gut. Because animal studies show that BAL may redistribute mercury to the brain from other tissue sites [76–78] and the brain is a target organ in elemental mercury poisoning, it would seem prudent not to use BAL for the treatment of inhalational exposures. DMSA appears to be associated with fever adverse events and more efficient mercury excretion when compared with d-penicillamine and is preferred for mercury vapor poisoning. DMSA may enhance urinary mercury excretion and reduce nephrotoxicity after GI absorption of elemental mercury [79]. The initial recommended dose of DMSA is 10 mg per kg every 8 hours, tapering to every 12 hours during the next several days. DMSA can be administered via nasogastric tube in severe poisoning cases in which endotracheal intubation is required.

The therapeutic end points of chelation are poorly defined. Probably the only objective measurable effectiveness of chelation therapy is enhanced urinary excretion of mercury. A potential end point for chelation may be when the patient's urinary mercury concentration approaches normal. Although the use of chelators is recommended to increase excretion and relieve target organs of metal burden, the use of BAL has not been proved to affect the course of elemental mercury-induced respiratory failure, and the effect of DMSA on clinical outcome has not yet been fully studied.

There is no role for multiple-dose activated charcoal, hemoperfusion, or hemodialysis in removing elemental mercury.

Inorganic Mercury

Acute inorganic mercury poisoning is usually the result of intentional or accidental ingestion. Most of the literature on inorganic mercury poisoning deals with mercuric chloride (mercuric bichloride [$HgCl_2$]), with the lethal adult dose estimated to be between 1 and 4 g.

Mercurials are available in medications (antiparasitic, antihelminthic, vermifuge, antiseptic, antipruritic, and disinfectant), paints, stool fixatives, permanent-wave solutions, teething powder, button batteries, fungicides/biocides, folk remedies (Mexican-American treatments for "empacho," a chronic stomach ailment; Asian, particularly Chinese, herbal or patent medications), and occult practices (Latin American and Caribbean natives). Although mercurial medications have largely been replaced by less toxic drugs, topical antiseptics containing mercury are still being used.

Pharmacology

Absorption of inorganic mercury salt from the GI tract is probably dose dependent. After absorption, the salt dissociates into the ionic form and is initially distributed between RBCs and plasma. Distribution of mercury within the body and within the organs varies widely. It has been demonstrated by animal autoradiographic study that mercuric ion is accumulated predominantly in the renal cortex [80]. Mercury ions do not appear to significantly cross the blood–brain barrier or the placental barrier. However, on the basis of the autoradiographic study, the brain does take up mercury slowly and retains it for a relatively longer period of time [80]. Mercury ions are eliminated from the body mainly by the urinary and fecal routes. The rate of excretion is dose dependent. Inorganic mercury follows a biphasic elimination rate, initially rapid and then slow, with a biologic half-life of about 60 days in humans.

Mercury ions have an affinity to bind and react with sulfhydryl moieties of proteins, leading to nonspecific inhibition of enzyme systems and pathologic alteration of cellular membranes. In addition, inorganic mercurials are highly corrosive substances.

The target organs of inorganic mercury poisoning are the GI tract and kidneys. The caustic property of the inorganic mercurials could potentially cause damage throughout GI tract, including corrosive stomatitis, necrotizing esophagitis, gastritis, and ulcerative colitis. A report of postmortem examination of patients who died within 48 hours postingestion showed severe hemorrhagic necrosis of the upper GI wall [81]. Nephrotoxicity following inorganic mercury poisoning from acute tubular necrosis of the distal portions of the proximal convoluted tubules resulted in acute oliguric renal failure and uremia [81,82]. The CNS is usually spared because only small amounts of mercuric ion can cross the blood–brain barrier. However, cases of CNS toxicity have been described with chronic mercury ingestion.

Clinical Toxicity

The clinical effects of acute inorganic mercury poisoning can be divided into the initial local corrosive effect on the GI tract followed by the injury that occurs at the site of excretion, which is the kidneys.

Inorganic mercury is a highly caustic substance. Depending on the amount ingested, the GI symptoms that follow may vary from mild gastritis to severe necrotizing ulceration of the intestinal mucosa, which can be fatal within a few hours [83]. Ingestion of 100 mg of inorganic mercury has been reported to be associated with a bitter metallic taste in the mouth, a sense of constriction about the throat, substernal burning, gastritis, abdominal pains, nausea, and vomiting [82]. A serious acute inorganic mercury ingestion may cause the abrupt onset of hematemesis, hemorrhagic gastroenteritis, and abdominal pain. Intestinal necrosis may ensue. In addition, massive bleeding from the colon has been reported to occur as late as 8 to 9 days postingestion [81]. Most of the bleeding came from the

rectum, which was the most severely involved section of the colon. Such injuries to the GI tract can lead to massive fluid, electrolyte, and blood loss, resulting in shock and death.

Acute inorganic mercury ingestion may lead to acute oliguric renal failure because of acute tubular necrosis. Invariably, those patients who develop renal involvement initially have severe GI symptoms [83]. Typically, oliguric renal failure occurs within 72 hours postingestion, and as such, the initial GI symptoms may be resolving while renal toxicity may not yet be [81,83]. Spontaneous resolution of acute toxic anuria with renal tubular regeneration may be expected to occur between 8 to 12 days [84], with clinical recovery (if it occurs) between 9 and 14 days [81,83]. Chronic exposure may result in CNS toxicity.

Diagnostic Evaluation

Diagnosis depends on integration of characteristic findings with a history of known or potential exposure and presence of elevated whole blood mercury concentration and urinary mercury excretion. Inorganic mercury may be visualized on an abdominal radiograph as radiopaque foreign bodies in the GI tract. A positive radiograph would support the diagnosis, but a negative one would not exclude it.

Whole blood and urinary mercury concentrations (see section "Elemental Mercury" of this chapter) are useful in confirming exposure. Whole blood mercury concentration greater than 50 µg per dL in acute inorganic mercury poisoning is often associated with gastroenteritis and acute renal tubular necrosis.

Management

General management considerations are the same as for elemental mercury poisoning. In patients with acute ingestion, GI decontamination should be performed as soon as possible to minimize absorption and decrease the corrosive effect of the ingested inorganic salt. As with the ingestion of any corrosive substance, inducing emesis is to be discouraged. Elective tracheal intubation may be prudent prior to attempting GI decontamination. Gastric lavage should be performed with caution as the GI tract may have already been severely damaged. Endoscopy is recommended if corrosive injury (drooling, dysphagia, and abdominal pain) is suspected. Although theoretically reasonable but not rigorously studied, the use of a protein gastric lavage solution (1 pint of skim milk with 50 g of glucose, 20 g of sodium bicarbonate, and three eggs beaten into a mixture) to bind the mercury has been suggested, along with rinsing the stomach with egg white or concentrated human albumin after the lavage [82]. Activated charcoal may be considered as 1 g of charcoal is capable of binding 850 mg of mercuric chloride [82].

In cases in which there is radiographic evidence of radiopaque foreign bodies in the GI tract and if there is no evidence of gastroenteritis, WBI with polyethylene glycol electrolyte solution should be considered. Repeat abdominal radiographs may be used to document the effectiveness of WBI.

GI injury may result in severe fluid, electrolyte, and blood loss, and attention should be given to monitoring the patient's volume status. Replace intravascular and GI losses by the appropriate administration of crystalloid, colloid, and blood product. An indwelling Foley catheter should be placed to carefully monitor the urine output, which should be maintained at 2 to 3 mL per kg per hour. It is important to distinguish between oliguria due to inadequate volume resuscitation and oliguria due to toxic nephropathy resulting in renal failure. Invasive hemodynamic monitoring may be necessary.

It should be remembered that inorganic mercury is a highly corrosive substance. Aggressive surgical intervention may be required in cases in which there is severe gastric necrosis or when hemorrhagic ulcerative colitis becomes life threatening [81,85]. It has been suggested that the rectum should be resected at the time of colectomy when it is indicated for controlling hemorrhage from the colon [81].

BAL and DMSA (see sections "Arsenic" and "Lead" of this chapter) are the chelating agents of choice. The effectiveness of BAL depends on the promptness of its administration and the administration of an adequate dose. BAL is most effective if given within 4 hours of ingestion [86]. Prompt intervention is paramount in reducing renal injury, so expedient chelation therapy would be prudent in suspected cases of acute inorganic mercury poisoning. Chelation should not be withheld while waiting for laboratory confirmation of mercury poisoning. DMSA is also effective, but the capacity of the GI tract to absorb orally administered DMSA may be very much impaired in cases of severe inorganic mercury poisoning when hemorrhagic gastroenteritis, hemodynamic instability, and splanchnic edema are present. Once the GI and cardiovascular status has been stabilized, chelation with DMSA may be substituted for BAL.

Once renal damaged has occurred from inorganic mercury poisoning, therapy should be directed at the acute renal failure that may ensue. Hemodialysis should be used to support the patient through the oliguric or anuric renal failure period. A potential problem arises with continued BAL therapy in patients who develop renal insufficiency because the kidneys are one of the main routes by which BAL-Hg is eliminated. In such circumstances, BAL therapy may be judiciously continued as there is some evidence from animal studies that a significant fraction of BAL-Hg is also excreted in the bile. Some studies indicate that hemodialysis may contribute to the elimination of BAL-Hg in patients with renal failure [87–89]. In a patient who has renal failure but is otherwise stable and has a functional GI tract, DMSA may be an alternative to BAL.

Organic Mercury

The organomercurials are compounds in which the mercury atom is joined to a carbon atom via a covalent bond. It is the relative stability of this covalent bond that determines the toxicology of the organic mercury compounds. The organomercurials can be classified as short-chain alkyl (methyl-, ethyl-, and propylmercury), long-chain alkyl, and aryl (phenyl) mercury compounds. In general, the short-chain alkyl group, particularly methylmercury, is considered the most toxic. Acute ingestion of 10 to 60 mg per kg of methylmercury may be lethal, and chronic daily ingestion of 10 µg per kg may be associated with adverse neurologic and reproductive effects.

Potential sources of exposure to organic mercury include herbicide, fungicide, germicide, and timber preservative. In the general population, the major source of exposure to methylmercury is through the consumption of predacious fish (e.g., pike, tuna, and swordfish). Major incidents of human poisoning with methylmercury have occurred (Minamata and Iraq epidemics) with devastating outcomes.

Pharmacology

Organic mercury antiseptics undergo limited skin penetration; however, in rare cases, such as topical application to an infected omphalocele, dermal absorption can occur.

Methylmercury is well absorbed after inhalation, ingestion, and probably dermal exposure. It is widely distributed throughout the body [90]. In the blood, more than 90% is found in the

RBCs, with whole blood-to-plasma ratios of 200:1 to 300:1 [91]. Methylmercury is present in the body as water-soluble complexes mainly attached to thiol ligands and is highly mobile. It enters the endothelial cells of the blood–brain barrier as a specific complex with l-cysteine. This l-complex is structurally similar to the large neutral amino acid l-methionine and carried across the cell membrane on the large neutral amino acid carrier [92]. Methylmercury is transported out of mammalian cells as a complex with reduced glutathione and is secreted into bile as a glutathione complex. The glutathione moiety is degraded in the bile duct and gallbladder and finally to the l-cysteine complex. It is reabsorbed and returned to the liver, thereby completing the enterohepatic cycle [93–95]. In humans, about 10% of the body's methylmercury burden is in the CNS and the biologic half-life of methylmercury is 45 to 70 days [96]. Methylmercury readily passes the blood–brain barrier as well as the placenta barrier [97]. In animal studies, the dissociation between the carbon and mercury bond of methylmercury is very slow [91], and phenylmercury undergoes rapid breakdown to inorganic mercury within 24 hours [90,98]. In humans, the major route of excretion of methylmercury is in the feces, with less than 10% appearing in the urine [99]. Extensive enterohepatic recirculation in the GI tract has been demonstrated to occur with methylmercury [100].

Mercury has an affinity to bind and react with sulfhydryl moieties of proteins, leading to nonspecific inhibition of enzyme systems and pathologic alteration of cellular membranes. The CNS is particularly vulnerable to the toxic effects of methylmercury and is a potent teratogen and reproductive toxin. Methylmercury has been shown to alter brain ornithine decarboxylase, an enzyme associated with cellular maturity, and neurotransmitter uptake at the pre- and postsynaptic adrenergic receptor sites [101].

Clinical Toxicity

Most of the detailed information regarding toxicity has been derived from methylmercury poisoning cases. Methylmercury is a cumulative poison, primarily affecting the CNS. There does not appear to be a distinct difference between acute and chronic methylmercury poisoning. Following acute methylmercury intoxication, symptoms are usually delayed for several weeks or months. The classic triad of methylmercury poisoning is dysarthria, ataxia, and constricted visual fields [102]. Other signs and symptoms include paresthesias, hearing impairment, progressive incoordination, loss of voluntary movement, and mental retardation. Perinatal exposure to methylmercury has caused mental retardation and a cerebral palsy type of syndrome in offspring. Ethylmercury compounds may also cause gastroenteritis. Phenylmercury compounds produce a pattern of toxicity intermediate between alkyl and inorganic mercury.

Diagnostic Evaluation

Diagnosis depends on integration of characteristic findings with a history of known or potential exposure, and presence of elevated whole blood mercury concentration, which may reflect recent exposure. Whole blood mercury concentrations greater than 20 µg per dL have been associated with symptoms. Hair concentrations have been used to document remote exposure. Urinary mercury concentrations are not useful.

Management

General management considerations are the same as for elemental mercury poisoning. Following acute ingestion of organic mercurials, gastric lavage should be performed. Administration of activated charcoal may be of benefit. A successful way to increase the rate of methylmercury excretion is to introduce a nonabsorbable mercury-binding substance (polythiol resin) into the GI tract so as to interrupt the enterohepatic recirculation of methylmercury [103,104]. Repeated oral administration of a polythiol resin in methylmercury intoxication may be beneficial.

Limited data suggest that oral neostigmine may improve motor strength in patients with moderate-to-severe chronic methylmercury intoxication [104]. DMSA is the preferred chelating agent. BAL has been ineffective in treating neurologic symptoms because of methylmercury poisoning [105]. In addition, animal studies show that BAL may redistribute mercury to the brain from other tissue sites [76–78]. In contrast, DMSA was effective in reducing the brain concentration of methylmercury [106], and DMSA prevented the development of cerebellar damage in methylmercury-poisoned animals [107]. However, in humans, the effect of DMSA on clinical outcome has not yet been fully studied.

Hemodialysis is of little value because methylmercury has a large volume of distribution, and a considerable amount of methylmercury resides within the RBCs.

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CHAPTER 134 ■ HYDROCARBON POISONING

WILLIAM J. LEWANDER AND ALFRED ALEGUAS JR

Hydrocarbons are a group of organic compounds composed primarily of hydrogen and carbon. Although often mixtures, hydrocarbons may be divided into four basic types: aliphatic, halogenated, aromatic, and terpene.

Hydrocarbon exposures are frequent and account for an inordinate number of health care visits and hospital admissions. The American Association of Poison Control Centers reported 54,766 hydrocarbon exposures in 2007 [1,2]. Twenty-two percent were seen in a health care facility, and there were seven deaths. Nearly 32% of total exposures occurred in children younger than 6 years of age and involved ingestions, and most of these were accidental.

Storage in unmarked, readily accessible containers and an attractive color or aroma account for the high percentage of exposures in young children. In adolescents and adults, poisoning generally results from inhalational abuse, occupational exposure, intentional ingestion, or accidental aspiration during the siphoning of fuels. Cutaneous and even intravenous exposures have also been described. Ingestions in adults usually involve larger volumes, and there is a much greater likelihood of other coingested drugs or toxins. The majority of deaths are due to intentional inhalation abuse.

ALIPHATIC HYDROCARBONS

Aliphatic hydrocarbons, known as petroleum distillates, are straight-chain compounds produced from the fractional distillation of natural petroleum (Table 134.1). They are the most common cause of hydrocarbon poisoning.

After ingestion, the major toxicity of petroleum distillates is their potential to cause a fulminant, and sometimes fatal, chemical pneumonitis. Aspiration of even small amounts may produce severe pulmonary toxicity. Although vomiting often precedes and precipitates aspiration, lack of vomiting does not preclude the possibility that aspiration has occurred. Little or no systemic toxicity occurs even with intragastric administration of large doses (12 to 18 mL per kg) [3,4].

The risk of aspiration increases with low viscosity, low surface tension, and high volatility. Viscosity, the tendency to resist flow, is the most important property determining aspiration potential [5]. Substances with low viscosity (e.g., gasoline, mineral seal oil, and kerosene) have a high aspiration potential, whereas those with high viscosity (e.g., mineral oil and fuel oil) have a low potential for aspiration. Reduced surface tension may also allow a substance to spread rapidly from the upper gastrointestinal (GI) tract to the trachea. High volatility (tendency of a liquid to become a gas) increases the likelihood of pulmonary absorption.

Aspirated petroleum distillates inhibit surfactant, resulting in alveolar collapse, ventilation–perfusion mismatch, and subsequent hypoxemia. In addition, bronchospasm and direct capillary damage lead to a chemical pneumonitis and hemorrhagic bronchitis–alveolitis [2,5,6]. In animals exposed to kerosene, acute alveolitis peaked at 3 days and resolved by 10 days [7]. Histologically, a chronic proliferative process occurred, peaking at 10 days and resolving over several weeks. When highly viscous petroleum distillates are aspirated, a less inflammatory but more localized and indolent lipoid pneumonia may occur [8].

TABLE 134.1

COMMON PETROLEUM DISTILLATES

Product	Synonym	Main use
Gasoline	Petroleum spirits	Fuel
Petroleum naphtha fluid	Ligroin	Cigarette lighter
VM and P naphtha thinner	Varnish naphtha	Paint or varnish
Mineral spirits	Painter's naphtha	Dry cleaner
	Stoddard solvent	Solvent
	White spirits	Paint thinner
	Varsol	
	Mineral turpentine	
	Petroleum spirits	
Kerosene fluid	Coal oil	Charcoal lighter
		Solvent
		Fuel for stoves, lamps
Fuel oil	Home heating oil	Fuel
Diesel oil	Gas oil	Furniture polish

Central nervous system (CNS) manifestations result principally from hypoxia and acidosis caused by pulmonary toxicity [9]. Although systemic toxicity is uncommon, it may be seen if the petroleum distillate is a vehicle for more toxic substances (e.g., heavy metal and pesticide), if it contains additives, or if a concomitant or massive ingestion has occurred [10]. Cardiovascular, hepatic, renal, and hematologic toxicities depend on the specific toxic substance involved.

Use of aliphatic hydrocarbons as volatile substances of abuse (VSA) is a serious and growing problem. It is most often seen in adolescents who use VSA as an easily available, legal, and affordable substitute for other intoxicants [11,12]. The most common aliphatic VSA are *n*-hexane, *n*-butane, isobutane, and propane—seen in adhesives, aerosols, liquefied petroleum gas (i.e., cigarette lighter refills and camp stoves), and gasoline. Inhalation may involve sniffing, "huffing" (spraying the solvent onto a cloth held to the mouth and nose), "bagging" (spraying the solvent into a paper or plastic bag and repeatedly inhaling the vapors), or a variant of these techniques [11]. These highly lipid-soluble substances are rapidly absorbed through the lungs and distributed to the CNS and fatty tissues [13]. The onset of symptoms occurs in seconds to minutes, with peak effects occurring somewhat later due to slower diffusion into tissues. Elimination of aliphatic hydrocarbon VSA is primarily by pulmonary excretion, and successive oxidation and metabolism by hepatic cytochrome P450 mixed-function oxidases [13].

Aliphatic VSA toxicity includes acute and chronic neurologic dysfunction; asphyxia; cardiovascular abnormalities; and pulmonary, GI, and cutaneous irritation. CNS toxicity ranges from stimulation at initial or low doses to a depressant effect, with general inhibition of cortical function at high doses [14]. Peripheral neuropathy and irreversible CNS damage have been reported [15–18]. Inhaled aliphatic hydrocarbons are asphyxiants (as well as pulmonary irritants) and may cause hypoxemia by decreasing the concentration of oxygen in inspired air. Their arrhythmogenic effects are thought to be due to their potentiation of endogenous catecholamines ("cardiac sensitization"), which may promote dysrhythmias (e.g., ventricular tachycardia or fibrillation) [19]. Additional factors such as hypoxia, acidosis, electrolyte abnormalities, and underlying cardiac conditions may contribute to arrhythmias. Dermal and mucosal irritation is due to their ability to dissolve lipids after prolonged or high-dose exposure [20]. Deaths associated with inhalational abuse may result from coma with respiratory depression, aspiration, or injuries incurred while intoxicated as well as from cardiac arrhythmias [21].

Clinical Manifestations

The clinical course after the ingestion of petroleum distillates primarily depends on the presence or absence of concomitant aspiration and its severity. Patients who aspirate generally demonstrate symptoms within 30 minutes; those who do not have symptoms within 6 hours of exposure remain asymptomatic [22]. Presenting signs and symptoms usually involve three main organ systems: pulmonary, CNS, and GI. Cardiovascular, renal, hematologic, and cutaneous toxicity have also been reported [23,24]. In most cases, symptoms resolve during the next 2 to 5 days with supportive care [22,25].

Initial coughing, gasping, and choking may progress and peak during the first 24 to 48 hours to tachypnea with grunting respirations, nasal flaring, retractions, and cyanosis [10,22]. The odor of petroleum distillates may be apparent on the breath. Wheezing, rhonchi, and rales may be heard on auscultation. In severe cases, pulmonary edema and hemoptysis occur. Arterial blood gases may demonstrate hypoxemia from ventilation–perfusion mismatch and early hypocarbia, which progresses to hypercarbia and acidosis. Abnormalities on chest radiographs occur in up to 75% of hospitalized patients, appearing within 2 hours in 88% of patients and by 12 hours in 98% [10,26], but may be delayed up to 72 hours. Early radiographic abnormalities include unilateral, but more commonly bilateral, basilar infiltrates and fine punctate perihilar densities. Localized areas of atelectasis are often present, whereas pleural effusions, pneumatoceles, and pneumothoraces occur infrequently [25,26]. Pneumatoceles generally occur 3 to 15 days after ingestion and resolve during 15 days to 21 months [2,27]. Radiographic findings correlate poorly with clinical symptoms and may persist for several days to weeks after symptoms have resolved [25–27]. Asymptomatic patients may have abnormal chest radiographs, whereas symptomatic patients may have minimal or no radiographic abnormalities early in the course [10].

Within the first 24 to 48 hours, fever (38°C to 39°C) and leukocytosis are common [22]. The persistence of fever beyond 48 hours suggests bacterial superinfection.

CNS involvement may occur in those with aspiration-induced hypoxemia, large intentional ingestions, or ingestions of mixtures that contain other toxic agents (e.g., aromatic hydrocarbons). Symptoms range from dizziness and lethargy (91%) to somnolence (5%) and, rarely, coma (3%) and convulsions (1%) [10,28]. The severity of CNS dysfunction often correlates with the severity of aspiration.

GI symptoms, such as local irritation of the oropharynx (e.g., burning), nausea, vomiting, and abdominal pain, are commonly reported. Hematemesis and melena occur rarely [10]. Vomiting appears to increase the likelihood of aspiration [25,29]. Cardiovascular toxicity is uncommon, but dysrhythmias and sudden death after gasoline siphoning have been reported [30].

Inhalation abuse may result in a range of acute CNS manifestations, including dizziness, incoordination, restlessness, excitement, euphoria, confusion, hallucinations, slurred speech, and coma with respiratory depression [31]. Peripheral neuropathy has been reported after chronic exposure [15,16]. Pulmonary toxicity may present as respiratory distress with cyanosis, or syncope with tachycardia or bradycardia. GI irritation may cause nausea, vomiting, and abdominal pain. Dermatologic manifestations range from perioral frost or pigmentation (after direct inhalation from a container) to local skin irritation [10].

Cases of acute renal tubular necrosis [32,33], hemoglobinuria secondary to intravascular hemolysis [34,35], severe burns after prolonged immersion in gasoline [36], and supraglottitis [37] have been reported. Aliphatic hydrocarbons are highly flammable, especially gasoline, and accidental thermal burns may occur during recreational use [38]. Therefore, patients with unexplained burns should be questioned regarding possible inhalation abuse. Chronic gasoline inhalation may also be accompanied by organo-lead poisoning [20,21,39]. Parenteral administration of petroleum distillates has caused local cellulitis, thrombophlebitis, and necrotizing myositis, with resultant compartment syndromes. Associated systemic effects include febrile reactions, hemorrhagic pneumonitis, pulmonary edema, seizures, and CNS depression [23,40,41].

Diagnostic Evaluation

After ingestion, diagnostic evaluation includes a thorough history (e.g., identity, amount, and concentration of toxin; time of ingestion; and symptoms before presentation at health care facility) and a physical examination (focusing on vital signs and the respiratory, CNS, and GI systems). Pulse oximetry should be monitored and a chest radiograph obtained in all symptomatic patients and in cases in which aspiration is suspected.

In symptomatic patients or those who have ingested concomitant toxins or toxic additives, laboratory evaluation should include an arterial blood gas determination; complete blood cell count; electrolyte, blood urea nitrogen, creatinine, and glucose measurements; liver function tests; and urinalysis.

Management

Patients with ingestions who remain or become asymptomatic with a normal chest radiograph (obtained 2 hours or more after exposure) may be discharged after 6 hours of observation. All symptomatic patients, those with abnormal chest radiographs, arterial blood gases, or pulse oximetry, and patients with suicidal intent should be hospitalized. Gastric decontamination is not recommended in petroleum distillate ingestion because absorption and systemic toxicity are minimal, and spontaneous or induced vomiting increases the risk of aspiration and pneumonitis [28,42]. Gastric decontamination is recommended only if potentially toxic amounts of aromatic or halogenated hydrocarbons, pesticides, heavy metals, or other substances have been ingested. Ipecac syrup is not recommended for GI decontamination. Patients who are unconscious, unable to protect the airway (e.g., poor or absent gag reflex), or deteriorating should be intubated with a cuffed endotracheal tube (in patients older than 6 years of age) and then have gastric aspiration or lavage performed. Activated charcoal and cathartic are indicated only if a toxic additive is present or concomitant ingestion has occurred. If cutaneous exposure has occurred, contaminated clothing should be removed and the skin thoroughly washed with soap and water [10].

All patients with respiratory symptoms should be given oxygen, placed on a cardiac monitor, and have intravenous access established. An arterial blood gas determination and chest radiograph should be obtained. The need for intubation should be based on clinical assessment of respiratory distress and objective data from arterial blood gases or pulse oximetry. Chest radiographs do not always correlate with clinical status and should not be used as the sole determinant for respiratory interventions. Continuous positive airway pressure may be necessary to maintain oxygenation, but the patient should be carefully monitored for the development of a pneumothorax. Bronchospasm should be treated with β_2-agonist bronchodilators because of potential myocardial sensitization to catecholamines [43].

Supportive care of pneumonitis includes careful monitoring of acid–base, fluid, and electrolyte balance (e.g., cautious hydration to avoid pulmonary edema), serial arterial blood gases or pulse oximetry, and chest radiograph evaluation. Complete blood cell counts with differential, serial sputum, or tracheal aspirate Grams stains and cultures assist in determining if bacterial superinfection has occurred. Baseline renal and liver function studies and a toxic screen should be obtained if toxic additives or concomitant ingestion is suspected. Animal and clinical investigations have failed to demonstrate any beneficial effect of steroid treatment [44,45]. Two animal studies indicate that they may be harmful [46–48]. In addition, prophylactic antibiotics have not been shown to be helpful [42,45,46]. Fever and leukocytosis secondary to chemical pneumonitis are common during the first 24 to 48 hours in the absence of superimposed bacterial pneumonia [10]. Antibiotics (e.g., penicillin or clindamycin) should be given only to patients with documented bacterial pneumonias (e.g., Grams stain or culture of sputum or tracheal aspirate) or worsening chest radiograph, leukocytosis, and fever after the first 40 hours [10]. Successful use of high-frequency jet ventilation and extracorporeal membrane oxygenation for the treatment of respiratory failure has been reported [49–51]. Other measures such as cardiopulmonary bypass, partial liquid fluorocarbon ventilation, and exogenous surfactant have been suggested for refractory cases, but the data to support their use are limited. [52,53].

Most patients with petroleum distillate poisoning recover fully with supportive care. Because minor pulmonary function abnormalities have been detected in as many as 82% of patients with aspiration pneumonitis who subsequently become asymptomatic [54], follow-up care with pulmonary function testing should be considered. When appropriate, the patient should receive psychiatric evaluation and poison-prevention education before final disposition.

HALOGENATED HYDROCARBONS

Halogenated hydrocarbons are aliphatic and aromatic derivatives that contain one or more atoms of chlorine, bromine, fluorine, or iodine. Although dozens of halogenated hydrocarbons are currently recognized, relatively few account for the majority of the toxic exposures. Like the aliphatic agents, halogenated hydrocarbons pose an aspiration risk. However, they are more readily absorbed from the GI tract and can cause systemic toxicity, most notably of the CNS, cardiovascular system, and hepatic and renal systems.

Halogenated hydrocarbons are used in the household and industry. They are frequently used as solvents, degreasers, dry-cleaning agents, refrigerants, aerosol propellants, and fumigants. Toxic exposures occur most commonly through inhalation, and several halogenated hydrocarbons (e.g., trichloroethylene, methylene chloride, and fluorocarbons) are intentionally inhaled for recreational purposes [55]. Bagging and huffing have been associated with a number of solvent-abuse deaths.

After absorption from the GI tract and occasionally through the skin, halogenated hydrocarbons are concentrated in adipose tissue, liver, and kidney. Metabolism and elimination vary according to the individual substance, with most undergoing at least some excretion through the lungs as unchanged parent compound and nearly all undergoing some degree of metabolism in the liver, with subsequent excretion of metabolites by the lungs and/or kidneys. Carbon tetrachloride (CCl_4), methylene chloride, and trichloroethane are prototypes of this class.

Carbon Tetrachloride

Previously used as a dry-cleaning agent and antihelminthic, CCl_4 is now restricted to industrial use, primarily in the production of refrigerants, aerosol propellants, and solvents. It is well absorbed through the skin [56], lungs, and GI tract, and it is concentrated in adipose tissue [57]. Approximately 50% of an absorbed dose is excreted unchanged by the lungs. Most of the remainder is metabolized by the liver to reactive intermediates or free radicals, or both, which covalently bind to proteins and induce lipid peroxidation, resulting in hepatocellular damage [58]. Ethanol, methanol, and isopropyl alcohol all increase CCl_4 hepatotoxicity, presumably through enzyme induction [59]. At lower doses, fatty degeneration of the liver occurs; at higher concentrations, centrilobular necrosis results [60]. In addition to hepatic damage, CCl_4 produces acute tubular necrosis of the kidney, affecting the proximal tubules and Henle's loop [61]. Although a direct nephrotoxic effect is likely [62], volume contraction may contribute to renal failure in some patients [63].

Inhalation exposure to CCl_4 may produce symptoms ranging from mild CNS depression to coma and death [64]. Although the estimated lethal dose of orally ingested CCl_4 is 90 to 100 mL, deaths have occasionally been reported after much smaller doses.

Nausea, vomiting, abdominal pain, diarrhea, drowsiness, and light-headedness usually occur within a few hours of exposure, regardless of route of exposure. Although liver enzymes may start to rise on the first day after exposure, clinical hepatotoxicity generally occurs on days 2 to 4, with fever, liver tenderness and enlargement, and jaundice [64]. Decline in renal function may occur concomitantly with hepatic dysfunction, although renal failure occasionally appears in the absence of hepatic failure [65]. Rarely, CCl_4 toxicity is accompanied by coma, convulsions, or myocarditis.

Early fatalities are the result of respiratory depression or cardiac dysrhythmias caused by cardiac sensitization to circulating catecholamines. Later deaths occur as the result of hepatic or renal failure, generally within the first week. In nonfatal cases, liver function tests generally return to normal within 2 weeks; recovery is usually complete.

Treatment initially involves stabilization and monitoring for respiratory depression and cardiac dysrhythmias. Exposure should be interrupted by removing victims of inhalation from the exposure site; in dermal exposures, contaminated clothing should be removed and the skin washed thoroughly. Patients who ingest more than 0.3 mL per kg should undergo gastric aspiration or lavage, preferably within 3 to 4 hours of ingestion [66]. Abdominal radiographs may be helpful in confirming suspected ingestions because CCl_4 is radiopaque [67]. There is no evidence regarding the use of activated charcoal in adsorbing CCl_4. Laboratory evaluation should include a complete blood cell count, routine serum chemistries, liver function tests, and urinalysis. Patients with respiratory symptoms or altered mental status should also be evaluated for possible aspiration pneumonitis, as described for aliphatic hydrocarbon exposures. Although CCl_4 appears not to be well removed by hemodialysis, dialysis may be required in cases of renal failure [68].

Animal studies suggest that hyperbaric oxygen may increase survival after intragastric administration of CCl_4 [69], although little human data exist on this topic [70,71]. Additional experimental work is being conducted to examine the utility of *N*-acetylcysteine in the reduction of CCl_4-induced hepatotoxicity. Because toxic intermediates of hepatic P450 are thought to be responsible for CCl_4 toxicity, it is thought that *N*-acetylcysteine may help prevent the development of liver failure [72,73]. Although human experience with this therapy is extremely limited in this setting and still considered experimental, a dosage schedule identical to that for acetaminophen is generally used.

Methylene Chloride

Methylene chloride is a colorless, volatile liquid commonly used as a solvent in aerosol products and as a degreaser and paint remover. It is well absorbed through the lungs and GI tract, but absorption through intact skin appears to be minimal. The majority of a dose is metabolized by the liver to carbon dioxide and carbon monoxide with small amounts exhaled unchanged [74].

The main toxicity of methylene chloride is CNS depression, which results from direct effects and from cellular asphyxia due to elevated levels of carboxyhemoglobin [75,76]. An 8-hour exposure to 250 ppm of methylene chloride resulted in carboxyhemoglobin fractions greater than 8% [77], and with large exposures, carboxyhemoglobin fractions up to 50% have been reported. In the few cases of methylene chloride ingestion that have been reported, CNS depression, tachypnea, and corrosive injury to the GI tract were the most common findings [78]. When the carboxyhemoglobin fraction is elevated, signs and symptoms of carbon monoxide poisoning may also be evident [79,80]. Nephrotoxicity and hepatotoxicity have also been reported [81,82].

Treatment involves stabilization, evaluation, and monitoring for aspiration, CNS and cardiovascular depression, dysrhythmias, corrosive injury, carbon monoxide poisoning, and hepatic and renal dysfunction. The patient should be removed from the source of inhalation exposure, and contaminated clothing should be removed. Exposed skin should be washed with soap and water. In cases of ingestion, gastric aspiration or lavage should be considered. The role of activated charcoal in methylene chloride ingestions is unclear [83]. In all cases, the carboxyhemoglobin fraction as well as complete blood cell count, routine serum chemistries, liver function tests, and urinalysis should be determined and supplemental oxygen provided.

Although hyperbaric oxygen is commonly used in cases of severe carbon monoxide poisoning, its role in methylene chloride toxicity is still being delineated [84,85]. It would appear reasonable to institute hyperbaric therapy when elevated carboxyhemoglobin levels are documented. Management is otherwise supportive.

Trichloroethane

1,1,1-Trichloroethane has been widely marketed as a safer alternative to CCl_4 for use as a cleaning agent and degreaser. It is also present in typewriter correction fluid and aerosol hairsprays, water repellents, and furniture polishes. In spite of its relative safety, death can occur, usually as a result of occupational or recreational inhalation exposure [86,87].

Trichloroethane is rapidly absorbed through the lungs and GI tract. Under most circumstances, significant cutaneous absorption is unlikely. Distribution is greatest to tissues with a high concentration of lipid, including the CNS. Most of an absorbed dose is excreted unchanged through the lungs, with smaller quantities metabolized in the liver and excreted by the kidneys [10].

Toxicity primarily involves the CNS, with signs and symptoms ranging from dizziness, headache, fatigue, and ataxia with mild-to-moderate exposures to seizures, coma, apnea, and death at higher vapor concentrations [88].

As with the aliphatic hydrocarbons, trichloroethane-induced cardiac sensitization to the effects of circulating catecholamines is thought to be responsible for sudden death associated with inhalational exposure [89,90]. Premature ventricular contractions and ST depression have been observed after acute inhalation [91], and myocarditis has been reported after chronic inhalation abuse [92]. Hepatic and renal toxicities are rare.

Management involves evaluation and treatment for aspiration, CNS and cardiovascular depression, and dysrhythmias. Decontamination measures may also be appropriate. In the absence of sudden death, recovery is generally rapid and complete.

AROMATIC HYDROCARBONS

Aromatic hydrocarbons contain one or more benzene rings. They include benzene, toluene, xylene, diphenyl, phenol, and styrene. Aromatic hydrocarbons are common constituents of glues, paints, paint removers, lacquers, degreasers, and adhesives. Although the aromatic hydrocarbons have aspiration risks similar to those of the other hydrocarbons, they also exhibit potentially severe systemic toxicity. Exposure is primarily through inhalation (occupational or abuse) or from ingestion. Benzene, toluene, and xylene are the three most commonly encountered agents.

Benzene

Benzene is a colorless liquid used widely in the chemical industry and less commonly as a solvent. It is well absorbed through the lungs and GI tract, but absorption through the skin is limited [93]. The lungs excrete up to 50% of an absorbed dose unchanged, whereas most of the remaining amount is metabolized by hepatic P450 enzymes to potentially cytotoxic metabolites [61,94]. Elimination of the parent compound and its metabolites generally occurs within 48 hours.

Benzene has acute and chronic toxicity [95]. Acute exposure primarily causes CNS depression [10]. Initial euphoria is rapidly followed by nausea, dizziness, and headache; subsequent progression to ataxia, seizures, and coma may occur. Persistent symptoms may include insomnia, anorexia, and headache.

Inhalation of high concentrations may lead to development of pulmonary edema; as with other hydrocarbons, aspiration and cardiac dysrhythmias may develop. Long-term exposure to benzene may result in a depression of bone marrow elements, which may progress to aplastic anemia [64,96]. Epidemiologic studies also suggest an increased risk of acute myelocytic and monocytic leukemia in workers with prolonged exposure to benzene [97,98].

Management should focus on stabilizing the patient and evaluation and monitoring for aspiration, CNS and cardiovascular depression, and dysrhythmias. It is generally agreed that amounts in excess of 1 to 2 mL per kg should be removed from the GI tract (via gastric aspiration or lavage), although some sources recommend removal of virtually any amount. The role of activated charcoal in this setting is unproved [10,99]. Subsequent therapy is supportive.

Toluene

Toluene is a colorless, volatile, sweet-smelling liquid that is a common ingredient in paints, paint thinners, lacquers, and glues (e.g., airplane model glue). Although toxicity may occur accidentally in industry or in the household, toluene is one of the most commonly abused solvents [100,101]. It is highly lipid soluble, and peak blood concentrations occur within 15 to 30 minutes with inhalation [64]. Animal studies suggest that ingested toluene is well absorbed from the GI tract, with 1 to 2 hours after exposure. Absorption through intact skin is slow.

Approximately 20% of an absorbed dose is exhaled unchanged. Most of the remainder is metabolized by the liver's cytochrome P450 system. Elimination is biphasic, with an initial alpha-phase having a half-life of 4 to 5 hours [102] and representing exhalation combined with distribution to fatty tissues [13]. The beta-phase has an apparent half-life of 15 to 20 hours and represents hepatic metabolism.

Toxic effects involve the CNS and peripheral nervous system as well as the kidney and heart [103]. Electrolyte and metabolic disturbances may also result. Acute exposure to toluene has variable effects on the CNS, depending on the concentration and duration of exposure [101,104,105]. Initially, toluene causes intoxication, which can progress to coma with prolonged exposure to high concentrations. Chronic abuse may also lead to persistent signs and symptoms of acute toxicity, including neuropsychiatric symptoms, weakness, nausea, vomiting, peripheral neuropathy, rhabdomyolysis [101], and abdominal pain [11]. Toluene toxicity is associated with a high incidence of renal dysfunction, particularly renal tubular acidosis (i.e., bicarbonate wasting) [101,106,107]. Laboratory findings include metabolic acidosis (with or without an increased anion gap), electrolyte disturbances (e.g., hypokalemia, hypocalcemia, hypophosphatemia, and hyperchloremia), and hematuria, proteinuria, and pyuria [106]. These abnormalities are the result of tubulointerstitial damage and are generally reversible on cessation of exposure. As with other hydrocarbons, acute toluene inhalation has also been associated with sudden cardiorespiratory arrest [108,109].

The diagnosis of toluene poisoning is generally made on the basis of the history, with known exposure or solvent abuse the prominent features. Toluene toxicity should also be considered in any individual with altered mental status and metabolic acidosis of unclear cause [110]. Management includes evaluation and treatment for aspiration; CNS and cardiovascular depression; dysrhythmias; renal dysfunction; fluid, electrolyte, and acid–base disturbances; and rhabdomyolysis. Laboratory testing should include calcium and phosphate levels. Gastric aspiration or lavage may be appropriate in cases of ingestion (with recognition of the aspiration risk).

Xylene

Xylene is a clear liquid that is widely used as a solvent in paints and lacquers, degreasers, adhesives, cleaning agents, and aviation fuel. It is rapidly absorbed by the pulmonary and GI systems and, to some extent, through the skin. The highest concentrations are found in the adrenal gland, bone marrow, spleen, brain, and blood [64]. Small amounts are excreted unchanged through the lungs; most of the remainder is metabolized in the liver and metabolites excreted in the urine. Ethanol consumption causes delays to metabolic clearance of xylene.

Xylene primarily affects the CNS [111]. As with other hydrocarbons, inhalation has been associated with sudden death, presumably secondary to cardiac dysrhythmia [112]. At low doses, headache, nausea, light-headedness, and ataxia may develop; at higher doses, confusion, coma, and respiratory depression may develop. Hepatic damage, Fanconi's syndrome, and pulmonary edema have also been described [112–114]. The evaluation and treatment of xylene exposure is similar to that described for other aromatic hydrocarbons.

TERPENES

Terpenes are aliphatic cyclic hydrocarbons. They include turpentine, pine oil, and camphor. Camphor is discussed elsewhere [10,115]. As its name suggests, pine oil is the product of pine trees and composed primarily of terpene alcohols. It is a component in household cleaners (e.g., Pine-Sol, Clorox Company, Oakland, CA), normally present in concentrations of 20% to 35%, but occasionally in concentrations exceeding 60%. Turpentine is a pine tree distillate commonly used as a solvent for paint and varnish.

Toxicity almost always results from ingestion. The aspiration risk appears to be somewhat less than that of other aliphatic hydrocarbons, presumably because of the lower volatility of terpenes; CNS and GI effects are more pronounced, however. Ingestions of more than 2 mL per kg of turpentine are considered potentially toxic [116]. Although 60 to 120 g of pine oil is commonly cited as the lethal dose in adults, survival has been reported after ingestion of 400 to 500 g [117]. The minimal lethal dose of pine oil reported in children is 14 g [118].

Turpentine is well absorbed through the lungs and GI tract [116] and distributed throughout the body, with highest concentrations in the liver, spleen, brain, and kidney [116]. Although the specifics of its metabolism are unclear, turpentine or its metabolites are largely excreted through the kidney. Pine oil is also well absorbed from the GI tract, and after absorption,

it is metabolized by the epoxide pathway and excreted in the urine [117]. Although the volume of distribution is unknown, it is thought to be quite large, with high concentrations in the brain, kidney, and lung.

Manifestations of toxicity include nausea, vomiting, diarrhea, weakness, somnolence, or agitation. In severe cases, stupor or coma may result, although seizures appear to be uncommon [119]. Systemic toxicity, when it occurs, usually develops within 2 to 3 hours of ingestion. In mild and moderate cases, GI and CNS symptoms generally resolve within 12 hours. Turpentine ingestion has been associated with hemorrhagic cystitis, with dysuria and hematuria occurring 12 hours to 3 days after exposure [120].

Management includes evaluation and treatment for aspiration, gastroenteritis, and CNS depression. The distinctive odors of turpentine and pine oil may provide a clue to diagnosis. Gastric aspiration or lavage is recommended for patients who present within 2 hours of ingesting greater than 2 mL per kg of turpentine or 5 mL of pure pine oil [121]. Because of the risk of aspiration, airway protection should be considered in all but the most alert patients.

Patients who remain asymptomatic or have only mild GI or CNS symptoms 6 hours after ingestion are unlikely to develop serious complications. Patients with pulmonary complications or severe CNS depression require intensive care unit admission and often require ventilatory support.

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CHAPTER 135 ■ HYDROFLUORIC ACID POISONING

KENNON HEARD

INTRODUCTION

Hydrofluoric acid (HF) is a commonly encountered industrial reagent that is available in concentrations from 6% to 90%. It is used for the production of fluorocarbons, etching glass, and silicone, and as a household rust-removal agent. Sodium fluoride is used as a rodenticide and also as a preservative in blood collection tubes. A related compound, ammonium bifluoride is used in rust removers, commonly found in commercial car washes.

MECHANISM OF ACTION

HF (pK_a = 3.8) is a weak acid. Hence, compared with other acids, it is relatively less ionized at any given pH. This allows HF to penetrate more deeply into tissue and to be more readily absorbed into the systemic circulation than other acids. Once absorbed, it disassociates and the fluoride anion binds to divalent cations, forming insoluble salts (primarily calcium fluoride, fluorapatite, and magnesium fluoride). This results in tissue and systemic hypocalcemia and hypomagnesemia. Fluoride also directly poisons several enzymes and cellular transport proteins. High-concentration HF exposures result in rapid onset of local pain and tissue injury with or without systemic toxicity, whereas low-concentration exposures can result in life-threatening hypocalcemia and hypomagnesemia, with minimal or absent local corrosive effect.

DERMAL EXPOSURE

Clinical Manifestations

While most dermal exposures will result in minor symptoms or superficial chemical burns, systemic toxicity may occur following dermal exposure. Symptoms may be delayed for 24 hours or more following low-concentration (< 20% HF) exposure, and there is often severe pain with minimal skin abnormalities. Symptoms can develop within several hours of exposure to medium concentrations (20% to 50% HF). While the initial injury is not always visible, patients exposed to medium-concentration products often go on to have erythema, blanching, or necrosis of the involved area. High-concentration (> 50% HF) exposures result in the immediate injury expected after exposure to concentrated acids. Patients may develop full- or partial-thickness injury that includes tissue necrosis and eschar formation [1].

Evaluation and Treatment

Laboratory studies are not indicated for small, low-concentration dermal exposures. However, exposure to products containing more than 50% HF that involve more than 1% of the skin or exposure to any HF product that affects more than 5% of the skin can cause hypocalcemia, so patients with these burns should have serum calcium levels monitored, as described in the systemic toxicity section below [2].

The most important step in treatment is decontamination by irrigating the affected area for at least 15 minutes as quickly as possible. In one large case series of exposures, many of which involved concentrations of greater than 40% HF, immediate irrigation produced excellent outcome in the majority of patients [3]. Hexafluoride, an irrigating solution developed to bind fluoride, does not appear to offer any improvement over water irrigation [4].

After irrigation, apply a 2.3% to 2.5% calcium gluconate preparation in a water-soluble gel to the exposed areas for at least 30 minutes or until symptoms resolve [5]. This treatment often remains effective if it is delayed several hours after symptoms develop [6]. The role of topical therapy following high-concentration exposures is less well defined, but it is recommended [7].

If pain is not relieved by topical therapy, regional intra-arterial or intravenous calcium perfusion should be initiated. The major drawback of intra-arterial perfusion is the requirement for arterial catheterization. Brachial, radial, and femoral catheterization have all been described. Following cannulation, monitor arterial waveform to assure that the catheter remains patent and properly placed within the artery. If there is any question as to adequate placement, perform arteriography prior to infusing calcium. Flushing the catheter with heparin may help keep the catheter patent [2]. The largest case series reported infusion of 50 mL of 2.5% calcium gluconate in saline over 4 hours [2]. It is not uncommon to have to repeat the dose several times over a 12- to 24-hour period.

Regional perfusion using a Bier block may allow treatment without arterial cannulization. Some clinicians advocate this technique before proceeding to intra-arterial administration. This technique requires venous cannulation in the affected extremity. The extremity is exsanguinated by elevation and compression with an Esmarch bandage. The blood pressure cuff should be inflated to a pressure 100 mm Hg above systolic pressure and remain up for 15 to 20 minutes following calcium administration. The usual dose is 40 mL of a 2.5% calcium gluconate solution [8]. The cuff is then gradually deflated over 5 minutes. Pain is usually relieved within minutes of the calcium administration.

If the affected area is not an extremity, calcium can be directly injected into the burn. The most common method is injection of 0.3 to 0.5 mL per cm^2 of 2.5% calcium gluconate. Calcium chloride should not be used as it can cause tissue injury. Excision of exposed tissue is not recommended.

OCULAR EXPOSURE

Clinical Manifestations

While most human reports describe good outcomes following ocular HF exposure, animal studies have demonstrated that

severe injury is possible. Although most patients have rapid onset of pain, HF can penetrate the eye and cause severe and delayed injury.

Evaluation and Treatment

Immediate irrigation is the most important treatment. Irrigation with calcium salts appears to offer no benefit over saline in animal models, and may increase the incidence of ulceration [9]. Following irrigation, the pH should be measured and a fluorescein examination should be performed. All patients with persistent symptoms or obvious corneal damage should have immediate evaluation by an ophthalmologist. Some will require admission for continuous irrigation. Patients who are asymptomatic after irrigation should have next-day follow-up with an ophthalmologist. Routine therapy for corneal burns from HF has included mydriatics, topical antibiotics, and steroids [10–12]. Treatment of these burns with calcium gluconate eyedrops has been suggested, but no systematic human studies have been reported [12].

INHALATION

Clinical Manifestations

Inhalation of HF may result in severe airway injury, pulmonary injury, and systemic fluoride poisoning. Patients may present with severe or minimal symptoms and go on to develop complications over time [13]. While systemic fluoride poisoning may occur [14], the major mechanism of pulmonary injury is acute lung injury.

Evaluation and Treatment

Following inhalation of HF, patients should have chest radiographs, evaluation of oxygenation, and monitoring for hypocalcemia. Treatment is supportive, and early airway intervention may be required for patients with symptoms of upper airway obstruction. There are several uncontrolled reports of good outcomes following treatment with nebulized calcium gluconate solution (2.5% to 5.0%) [15,16].

INGESTION

Clinical Manifestations

Oropharyngeal burns are rarely noted, even in fatal poisonings [17]. While gastrointestinal symptoms such as nausea, vomiting, and gastritis may occur, the primary manifestation of oral HF exposures is systemic fluoride toxicity (see below). Following accidental sip ingestions, patients who are able to swallow should be given 30 to 60 mL of water to drink to dilute any HF still in contact with the esophageal mucosa. While it is commonly recommended to administer calcium or magnesium antacids, animals studies have found that very high doses are required to affect mortality [18,19]. Patients with accidental ingestion of products containing more than 7% HF or deliberate ingestion of any HF or ammonium fluoride product are at risk for systemic poisoning and require continuous cardiac monitoring, reliable vascular access, and close monitoring of serum calcium levels, as described in the next section.

Systemic Toxicity

Systemic fluoride toxicity may occur following inhalation and dermal or oral exposure to HF-containing products. While the exact mechanism of fluoride toxicity requires continued research [20], human cases of fatal HF toxicity consistently demonstrate profound hypocalcemia) [21]. Other manifestations include hypomagnesemia, acidosis, and hyperkalemia. Minimally symptomatic patients may progress rapidly to cardiovascular collapse [22].

Because successful resuscitation from cardiac arrest following systemic fluoride poisoning is rare, treatment should be started early to prevent cardiac dysrhythmias and arrest. Patients should have continuous cardiac monitoring, reliable vascular access, and frequent measurement of serum calcium and magnesium. If the history suggests that there has been a significant exposure, prophylactic calcium should be initiated at a rate of 1 g over 30 minutes [20]. Patients who have normal vital signs and remain stable should have serum calcium levels monitored every 30 minutes for the first 2 to 3 hours. Calcium chloride 1-g boluses should be repeated as needed to maintain the serum calcium in the high normal range. Patients with hypocalcemia, dysrhythmias, or hypotension should receive 2 to 3 g of calcium every 15 minutes, and central venous access should be obtained. Successful treatment of cardiac arrest has generally been associated with administration of large doses (> 10 g) of calcium. Intravenous magnesium sulfate 2 to 6 g over 30 minutes followed by a continuous 1- to 4-g infusion has also been suggested.

Beyond calcium and magnesium administration, fluoride-poisoned patients require excellent supportive care. Patients with symptoms of airway involvement should be intubated. Similarly, ventilation and oxygenation problems are rare but should be treated aggressively if present. Successful electrical cardioversion for dysrhythmias following calcium and magnesium therapy has been reported [23].

A therapy that is unproven but has theoretical benefit is serum and urine alkalinization. One animal study showed that systemic alkalosis increased the fatal fluoride dose in rats [24]. While this study has obvious limitations, serum alkalinization should be considered in critically ill patients. However, overalkalinization may worsen hypocalcemia; therefore, serum pH should be maintained between 7.4 and 7.5. While fluoride is cleared by hemodialysis, patients with severe poisoning will be too unstable to be dialyzed.

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CHAPTER 136 ■ IRON POISONING

MILTON TENENBEIN

Historically, iron poisoning is the most common cause of poisoning death in children younger than 6 years [1]; however, morbidity and mortality have decreased secondary to unit-dose packaging of iron supplements [2]. Notably, a clinically important proportion of iron overdoses is purposeful, involves adolescents and adults, and results in significant morbidity and mortality [3].

Iron occurs naturally in the body. It is highly reactive, and there are complex mechanisms for its absorption, transport, and storage. The capacity of these systems to cope with an acute overdose is unknown; it likely varies from individual to individual and with the state of iron stores. Incomplete understanding of iron toxicokinetics is primarily responsible for controversies regarding (a) the toxic dose; (b) the optimal method of gastrointestinal decontamination; (c) the efficacy of intragastric complexation therapies; and (d) the indications, dose, duration, and efficacy of deferoxamine therapy.

PHARMACOLOGY

Iron is readily available as ferrous salts, either alone or in combination with other minerals and vitamins. Its common salts are ferrous gluconate, sulfate, fumarate, and succinate, which are 12%, 20%, 33%, and 35% elemental iron, respectively. These fractions are important because toxicity is related to the amount of elemental iron ingested. Iron is marketed in both conventional and delayed-release formulations. Product labels may not specify the tablet formulation, an important determinant of the onset and duration of toxicity. Carbonyl iron is a highly purified form of metallic iron. It is uncharged and not a salt [4].

Iron absorption, transport, and storage are well reviewed elsewhere [5]. Because there is no endogenous mechanism for iron excretion, total body iron is a function of the absorptive process. Absorption occurs in the proximal small bowel, with approximately 10% of the ingested dose absorbed, but with tenfold variations depending on iron stores and the amount ingested. The actual mechanism of iron absorption is not well understood, but it is believed to be an active process. Iron can also be passively absorbed once the active process is saturated, such as after a massive overdose [6]. Even in such a situation, a relatively small amount (15%) is actually absorbed [6].

Peak serum iron concentrations occur within 4 to 6 hours after an overdose of conventional tablets. The time to peak serum concentration is not known for delayed-release products. The half-life after therapeutic dosing is approximately 6 hours [5], with rapid decline because of tissue distribution. In plasma, iron is bound to transferrin, a specific β_1-globulin responsible for iron transport throughout the body. In iron overdose, transferrin-binding capacity is exceeded, but free plasma iron does not truly exist. Iron complexes with other plasma proteins and organic ligands and is referred to as *nontransferrin-bound plasma iron* [7]. However, it is only loosely bound and is quite available to produce tissue damage and organ dysfunction.

There are two typical overdose scenarios: innocent overdose by young children and purposeful overdose by adolescents and adults. Serious iron overdose in young children frequently involves the ingestion of a product intended for adults, typically a prenatal iron supplement. Ingestion of pediatric preparations, such as multivitamin plus iron tablets, is more common [8]; such preparations are unlikely to result in significant toxicity because of their low elemental iron content (as little as 4 mg per tablet). Although liquid iron preparations are often found in homes with infants and toddlers, there are no published cases of clinically important iron poisoning because of these products. Iron overdose is less common among teenagers and adults, but when it occurs, it is typically more severe. Of particular note is the high incidence of deliberate iron overdose in pregnant women [9].

Iron exerts both local and systemic effects. The local irritant effect on the gastrointestinal tract results in nausea, vomiting,

abdominal cramps, and diarrhea. These symptoms are produced by relatively small doses (20 mg per kg of elemental iron). The degree of systemic toxicity is, however, dose related. Because most published data are anecdotal, specific values have not been established. In the pediatric literature, more than 60 mg per kg of elemental iron produces significant systemic toxicity [10], with a lethal dose being 200 to 250 mg per kg [10]. Both the figures are likely overestimates; more realistic figures are probably half as much. The lowest reported lethal dose for a toddler is approximately 75 mg per kg of elemental iron [11]. The author's own experience and that of others [12] suggests that the range of toxicity in adults is similar to that in children. An ingestion of 1.5 g of elemental iron by an adult should be cause for concern. Adults have died after ingestion of as little as 2 [13] and 5 g [12] of elemental iron; the former patient had significant hepatic disease and the latter ingested 70 mg per kg. There have been no published reports of serious or fatal poisoning from the ingestion of carbonyl iron products [4]. Although its bioavailability after therapeutic dosing is similar to ferrous salts, its absorption is limited after an overdose. Single doses of 10 g (140 mg per kg) have been tolerated in humans.

Poor, unpredictable absorption of iron and its unknown capacity for binding by ferritin and as hemosiderin contribute to uncertainty regarding the toxic dose. As reflected by serum iron concentrations, which are measured in micrograms per deciliter, the size of the potentially toxic iron pool is likely to be small—on the order of milligrams—even after gram quantities of iron have been ingested. That the body burden of iron is relatively small after an overdose is not well appreciated, but it has important implications for the dose and duration of deferoxamine therapy.

Iron itself is neither caustic nor corrosive. It is a potent catalyst of free radical formation, which results in highly reactive species that attack many intracellular molecules [14]. Iron-generated free radical formation is thought to contribute to acute iron toxicity [15] and to be responsible for much of the damage and dysfunction of chronic iron overload [7].

Free radicals produce damage at their site of origin. Because of local protective mechanisms, a significant concentration of free radicals is required to cause damage. Sites exposed to high iron concentrations are most susceptible to injury. One such area is the gastrointestinal tract. Gastrointestinal mucosal necrosis and bleeding [16] may occur without systemic toxicity. Notably, gut toxicity can occur distally with proximal sparing [16] and may be absent in the face of fatal systemic poisoning [6].

Systemic toxicity results when the absorbed iron is transported to target organs, such as the liver and heart. Nontransferrin-bound iron is rapidly cleared by the liver [17], putting this organ at risk for toxicity [18].

CLINICAL TOXICITY

Traditionally, acute iron intoxication is divided into five clinical stages [19]: gastrointestinal toxicity, relative stability, circulatory shock, hepatic necrosis, and gastrointestinal scarring. An orderly progression through all these stages may not occur. Fatalities are possible without significant gastrointestinal involvement [6], and hepatotoxicity may be absent in otherwise severe poisoning. Presenting signs and symptoms depend on the time since ingestion.

The most common time of presentation is during the first stage (gastrointestinal toxicity), when abdominal pain, vomiting, diarrhea, hematemesis, and hematochezia are seen. Gastrointestinal toxicity usually occurs within the first few hours of overdose. If enteric-coated tablets have been ingested, gastrointestinal toxicity can be delayed as long as 12 hours. The severity of this stage is variable. Life-threatening hypovolemic shock may occur, especially if initial symptoms were severe or ignored. Occasionally, segmental intestinal infarction may occur, necessitating bowel resection [16]. Isolated hepatotoxicity or gastrointestinal obstruction would be an unlikely presentation of iron poisoning.

The second stage, a period of relative stability, follows initial gastrointestinal symptoms. Apparent improvement in the patient's clinical status should not lead to complacency. Patients are not completely asymptomatic; careful assessment and repeated monitoring should document some degree of hypovolemia, circulatory shock, and acidosis.

The third stage, circulatory shock, can occur within several hours of iron overdose and may persist up to 48 to 72 hours. Its pathogenesis is complex and poorly understood and is based on the results of limited experimental animal data [20–23]. Circulatory shock may be hypovolemic, distributive, or cardiogenic. The time of onset can be somewhat helpful in elucidating its cause, but there is considerable overlap. Shock occurring within a few hours of the overdose suggests hypovolemia secondary to fluid and, rarely, blood loss from the gastrointestinal tract. Hyperferremia-associated coagulopathy may contribute to bleeding [24]. Distributive shock depends on iron absorption and begins within the first 24 hours. Suggested mechanisms include direct effects of iron or ferritin or an effect mediated by release of vasoactive substances, resulting in decreased vascular tone or increased vascular permeability [22]. Cardiogenic shock usually occurs 1 to 3 days after overdose [25].

The occurrence of metabolic acidosis in iron poisoning usually precedes circulatory shock. Acidosis is a direct toxic effect of iron that occurs after the plasma's capacity to bind the absorbed ferric ion has been exceeded. When this occurs, the ferric ion becomes hydrated and protons are released [$Fe^{3+} + 3H_2O \rightarrow Fe(OH)_3 + 3H^+$]. Thus, each unbound ferric ion generates three protons. The acidosis can be quite profound, requiring large amounts of bicarbonate for treatment [23]. Other factors contributing to acidosis include the generation of organic acids resulting from iron's interference with intracellular oxidative metabolism and lactate production secondary to shock.

The fourth stage, hepatotoxicity, is second only to shock as a cause of death [18]. It may occur any time during the first 48 hours after overdose. The pathogenesis of hepatic necrosis is believed to be iron-catalyzed free radical production and subsequent lipid peroxidation of hepatic mitochondrial membranes [15].

The fifth stage, gastrointestinal scarring, is the consequence of iron's local action on the gut and usually occurs 2 to 4 weeks after overdose. Ongoing and protracted abdominal pain during the first week is associated with the later development of this complication [16]. Most cases involve the gastric outlet, but isolated strictures of distal intestine have been reported [16].

The consequences of iron poisoning in pregnant women are no different from those in other patients, but because transplacental iron passage is an energy-requiring saturable process, the fetus is relatively protected [26]. Although deferoxamine in animals is associated with potential harm to the fetus, its risk in humans is overemphasized [26]. The health of the fetus depends on its mother, and treatment should be no different from that given to a nonpregnant woman.

DIAGNOSTIC EVALUATION

Essential laboratory tests include abdominal radiographs, serum iron and bicarbonate concentrations, and blood gas determinations. Because iron tablets are radiopaque, an abdominal radiograph can be used to verify an overdose and quantify

the amount ingested [27–29]. However, iron tablets may not be visible if they have dissolved or been chewed, a liquid preparation has been ingested, or there is only a small amount of iron in each tablet (e.g., pediatric iron-containing multivitamins) [30]. If tablets are visible, serial abdominal radiographs may be used to judge the effectiveness of gastrointestinal decontamination.

Serum iron concentration is the single most important test. It verifies the ingestion, guides management, and provides prognostic information. A peak serum concentration of less than 500 µg per dL (90 µmol per L) is usually associated with negligible-to-mild systemic toxicity; however, there may be significant gastrointestinal symptoms. Moderate systemic toxicity is expected with a peak concentration of 500 to 1,000 µg per dL (90 to 180 µmol per L). A peak serum concentration greater than 1,000 µg per dL (180 µmol per L) is associated with severe toxicity, such as profound acidosis, shock, hepatotoxicity, coma, and death. Mortality approaches 100% when serum concentration is greater than 10,000 µg per dL (1,800 µmol per L). The time of blood sampling to estimate peak serum iron concentration should be 4 to 6 hours after an overdose of conventional tablets and several hours later for an overdose of delayed-release formulations. However, the type of preparation ingested is usually unknown at the time a patient seeks treatment and is difficult to establish even after the fact [31]. Serial serum iron concentration determinations are recommended during the early hours after overdose, especially when the first value is 300 to 500 µg per dL (55 to 90 µmol per L). Determinations should be obtained every 2 hours until a definite downward trend is established. A concurrent abdominal radiograph may be helpful. If many tablets are visible, the subsequent serum iron level will likely be higher. However, a negative radiograph does not guarantee that peak serum iron level has occurred. It is desirable to obtain blood specimens before initiating deferoxamine therapy because it can confound the laboratory determination of serum iron concentration, resulting in falsely lower levels [32]. When clinically indicated, deferoxamine therapy should not be delayed because of blood sampling issues.

Blood gas or serum bicarbonate determinations should be done early because acidosis is the first objective indicator of systemic toxicity. Frequency of blood gas determinations is guided by previous values, the need for bicarbonate therapy, and clinical course. A pH of less than 7.30 is indicative of significant toxicity.

Recommended laboratory tests include blood coagulation panels and hepatic and renal function tests. Blood coagulation panels should be done early and repeated throughout the first few days in patients with significant toxicity because a biphasic coagulopathy may develop [24]. Blood should be typed and cross-matched as clinically indicated. Hepatic function should be monitored daily during the first 72 hours and longer if values remain significantly abnormal. Renal function tests should be obtained regularly, especially during deferoxamine therapy, because of the risk for acute renal failure [33].

The total iron-binding capacity (TIBC) is not recommended in the assessment or management of patients with iron overdose [34]. Routine methods for TIBC determination are unreliable during hyperferremic states and are time consuming [34]. The TIBC becomes falsely elevated in the presence of high serum iron concentrations, and it has yet to be demonstrated that iron toxicity occurs only when the serum iron concentration exceeds the TIBC [34]. A serum iron concentration that is less than the TIBC does not rule out acute iron poisoning.

One retrospective study of acute iron overdose showed that vomiting was a highly sensitive predictor of a serum iron concentration greater than 300 µg per dL (54 µmol per L). In addition, a white blood cell count greater than 15,000 per µL or a serum glucose concentration greater than 150 mg per dL (8.3 mmol per L) has a positive predictive value of 100% for a serum iron level greater than 300 µg per dL (54 µmol per L) [35]. However, these tests have unacceptably low sensitivity and negative predictive value. Although such surrogate markers may be helpful when serum iron concentrations are not readily available, these associations have not been confirmed in subsequent studies [36,37]. The absence of vomiting, a white blood cell count less than 15,000 per µL, or a serum glucose concentration of less than 150 mg per dL (8.3 mmol per L) should not be relied on as a surrogate marker for a serum iron level of less than 300 µg per dL (54 µmol per L).

It is difficult to accurately predict outcomes because the published literature chiefly consists of anecdotal reports. Survival is expected with peak serum iron concentrations of less than 1,000 µg per dL (180 µmol per L) and appropriate supportive care. The chief causes of death are shock and hepatic failure. Acute renal failure may result from shock or deferoxamine therapy without adequate volume replacement [33]. *Yersinia septicemia* has been reported in patients treated with deferoxamine [27,38].

Differential diagnosis becomes an issue only when the history of iron overdose is unknown. In such situations, diagnosis can be quite problematic because of the multiple and varied clinical features at presentation (e.g., abdominal pain, gastrointestinal hemorrhage, shock, and coma). From the poisoning perspective, corrosive ingestion and acute heavy metal poisoning are the main considerations.

MANAGEMENT

The initial management of a patient with an iron overdose presents a challenge because the patient often presents before the peak of clinical toxicity. Many patients, especially young children, may be asymptomatic or only mildly ill. The challenge lies in identifying those who are at risk for significant toxicity in order to place them in an appropriate setting for the required level of care. The decision for the iron-overdosed critically ill patient is straightforward. Table 136.1 provides guidelines for intensive care unit admission for those patients who are not critically ill.

TABLE 136.1

SUGGESTED CRITERIA FOR ADMISSION OF THE NONCRITICALLY ILL IRON-OVERDOSED PATIENT TO AN INTENSIVE CARE UNIT

	Admit to ICU	Strongly consider admission to ICU
Amount of elemental iron ingested		
Child (< 6 y)	> 60 mg/kg	45–60 mg/kg
Adult (all others)	> 3.0 g	2.0–3.0 g
Tablets seen in radiograph[a]		
Child (< 6 y)	1/kg	0.75–1.00/kg
Adult (all others)	> 50	33–50
Peak serum iron concentrations	> 1,000 µg/dL (> 180 µmol/L)	750–1,000 µg/dL (135–180 µmol/L)
Arterial pH	< 7.30	7.30–7.35

[a] Assuming 60-mg elemental iron/tablet.
Note: Not all criteria need to be present.

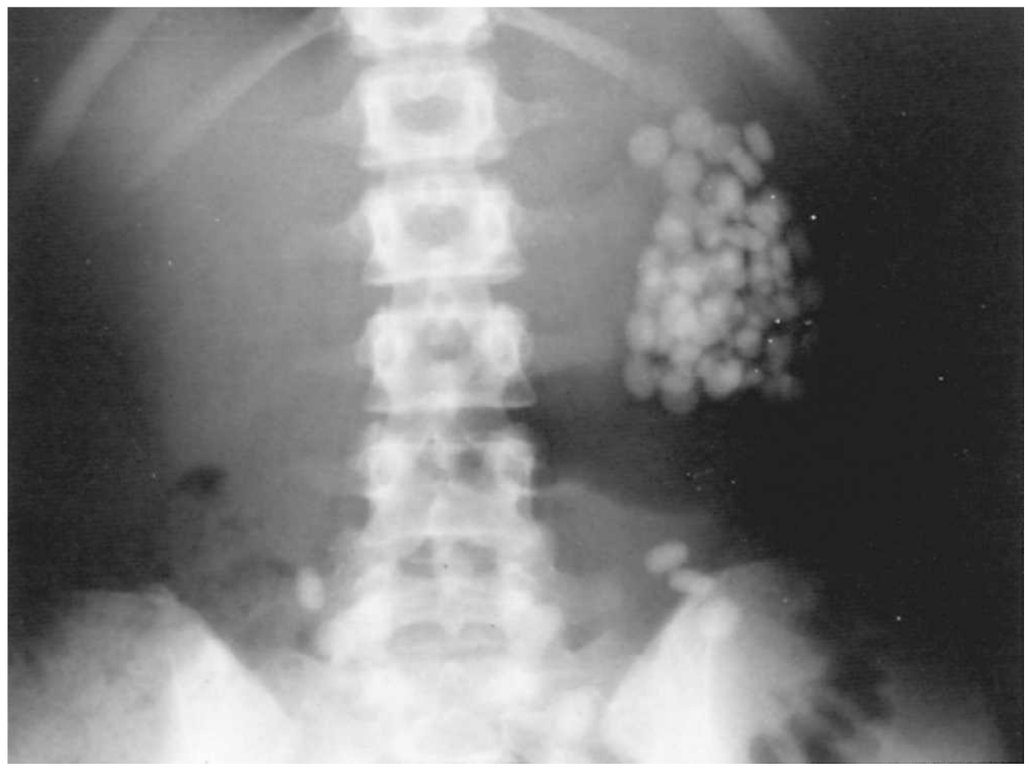

FIGURE 136.1. Abdominal radiograph of a 16-year-old girl with a potentially lethal iron overdose after syrup of ipecac-induced emesis and gastric lavage. Gastroscopy ruled out adherence of iron to the stomach wall and medication concretion. She subsequently underwent whole-bowel irrigation. Her peak serum iron concentration was 253 µg per dL (46 µmol per L), and she was not treated with deferoxamine.

Because activated charcoal does not adsorb iron [28], whole-bowel irrigation (WBI; Fig. 136.1) is recommended as the decontamination procedure of choice for the iron-overdosed patient [29]. WBI should be initiated when there is radiographic documentation of iron ingestion and considered when there is a history of elemental iron ingestion greater than 60 mg per kg in children and 1.5 g per kg in adults. If emesis hampers effective WBI, consider metoclopramide (1 mg per kg intravenously in adults and 0.1 mg per kg in children) or ondansetron (8 mg per kg intravenously in adults or 0.1 to 0.2 mg per kg in children).

Iron can become adherent to the gastrointestinal mucosa or may form tablet bezoars [39]. The latter is primarily a problem with conventional iron tablets and not with the enteric-coated varieties. Radiographs in three planes (flat, upright, and decubitus) should identify these two situations. A computed tomographic (CT) scan is another consideration. Barium studies are unlikely to be helpful because of the anticipated lack of contrast between barium and iron. If WBI is ineffective, removal of iron via gastrotomy should be considered [39,40]. For surgical intervention to be effective, it should be done before the iron is absorbed and most tablets must be in a localized area rather than scattered throughout the gastrointestinal tract. A combined approach of gastrotomy for tablet retrieval followed by WBI after surgery has been described [40]. The former removed the iron from the stomach and the latter removed it from the intestinal tract. Endoscopic removal of an iron bezoar from the stomach has been reported [41].

The oral administration of bicarbonate, phosphate, or deferoxamine is not recommended. These agents have been advocated as a way to decrease iron absorption by precipitating it as an insoluble salt or by chelating it. In vitro [42] and animal [43] studies do not support bicarbonate or phosphate administration, and the latter therapy has resulted in hypocalcemia and hypovolemia in iron-overdosed patients [44]. Oral deferoxamine is not recommended. It is neither appreciably toxic nor absorbed from the gastrointestinal tract, but the same is not true of its chelate, ferrioxamine [19,21,45]. The latter has been shown to be lethal in animals [21,46].

Supportive care should be provided concurrently with gastrointestinal decontamination. In patients with severe poisoning, two intravenous (IV) lines are required: one for fluid resuscitation and bicarbonate administration and the other for deferoxamine therapy. Very large amounts of crystalloid and bicarbonate may be required [23], and occasionally, colloid or blood may be necessary. Because of the complex nature of shock in iron poisoning, early placement of a Swan-Ganz catheter may be needed to assist in diagnosis and monitor the effectiveness of therapy. Early shock should respond to vigorous volume resuscitation; occasionally, pressor therapy may be needed. Late shock usually requires inotropic support. Failure of inotropic support suggests the need for afterload reduction [25]; once a patient has reached this point, the prognosis is grave. An arterial catheter for frequent blood gas determinations and a Foley catheter for monitoring urine output are essential in all critically ill patients.

Parameters requiring serial monitoring include arterial blood gas, hematocrit, serum electrolytes, renal and hepatic function, and blood coagulation. The frequency of these determinations depends on previous results and the patient's clinical condition and response to the therapy.

Acute hepatic failure is managed by standard protocols. Acute renal failure may be a consequence of shock or deferoxamine therapy in the setting of hypovolemia [33]. Hemodialysis may be required in such situations, especially if deferoxamine therapy is continued, to remove the toxic chelate, ferrioxamine. Coagulopathy during the first few hours after overdose is related to serum iron concentration and is transient. Specific therapy is unnecessary. Deferoxamine lowers the serum iron concentration and may hasten its resolution [24]. Coagulopathy occurring many hours to a few days after overdose is a manifestation of hepatic failure. Administration of fresh-frozen plasma is recommended, as vitamin K_1 is unlikely to be helpful.

Hemodialysis or hemoperfusion is not recommended for iron removal because of the rapid extravascular distribution of the iron and its binding to plasma proteins as nontransferrin-bound iron [7]. However, hemodialysis is indicated for patients with renal failure.

Deferoxamine, the specific treatment of choice for acute iron poisoning [15,19], is a naturally occurring siderophore isolated from *Streptomyces pilosus*. Its pharmacology was described in the early 1960s [47,48]. Its binding constant for ferric iron is 10^{31}, which compares with 10^{27} to 10^{29} for transferrin. It is capable of removing iron from ferritin and hemosiderin and, to a very minor degree, from transferrin, but not at all from cytochromes, hemoglobin, or myoglobin.

Although deferoxamine is regarded as the treatment of choice, its effectiveness has been questioned because it has limited chelating capacity and only small amounts of iron are recovered in the urine after its administration to iron-poisoned patients [49]. The manufacturer's recommended daily deferoxamine dosage of 6 g is capable of chelating 510 mg of iron or 8.5 ferrous sulfate tablets. Although this would seem to be insignificant in the patient who has ingested 50 tablets, the poor absorption of iron and the body's large storage capacity for it result in only a relatively small amount being responsible for toxicity. Therefore, the chelation of small amounts of iron may be quite beneficial. Alternatively, 510 mg of iron is approximately 10% of the total amount of iron and approximately 35% of the nonheme iron in a 70-kg man [50].

Historically, therapy was based on the deferoxamine chelation challenge test and relied on visual detection of a change in urine color to rusty orange (vin rosé) caused by the presence of ferrioxamine after intramuscular administration of deferoxamine. This test has never been validated and is not recommended.

Traditional indications for deferoxamine therapy have been based on the peak serum iron concentration, the serum iron concentration relative to the TIBC, the results of a chelation challenge test, and the patient's clinical condition. The therapy has been recommended for those with peak serum iron

concentrations ranging from 300 to 500 µg per dL (55 to 90 µmol per L) [51]. Significant morbidity is unlikely with peak concentrations of less than 500 µg per dL (90 µmol per L). Values at the lower end of the above range are based on the upper limit of normal for TIBC, which, as discussed earlier, is invalid. Hence, a serum iron concentration of 500 µg per dL (90 µmol per L) or greater is recommended as an indication for deferoxamine therapy in an otherwise asymptomatic patient. Deferoxamine therapy is indicated when toxic signs and symptoms are present, regardless of the serum iron concentration. Such symptoms include acidosis, shock, and decreased level of consciousness or coma. Although some toxicologists also advocate deferoxamine therapy for those with recurrent vomiting or diarrhea, these symptoms can be seen in patients who do not develop systemic toxicity.

Deferoxamine can be given intravenously or intramuscularly. The manufacturer recommends intramuscular therapy unless the patient is in shock, presumably because of concern for hypotension, which is associated with rapid IV administration. The patient should be fluid resuscitated, and IV deferoxamine therapy should be initiated slowly and gradually increased to 15 mg per kg per hour during 20 to 30 minutes. Continuous IV infusion is the recommended method for administering deferoxamine. This is based on studies in patients with transfusion-induced iron overload, demonstrating that IV deferoxamine results in greater urinary iron elimination, higher peak deferoxamine serum concentrations, and more stable serum deferoxamine levels [52].

The optimal dose of deferoxamine is uncertain. The manufacturer recommends a daily maximum dose of 6 g given in divided doses. A continuous infusion protocol of 15 mg per kg per hour until 24 hours after the urine returns to its normal color has also been recommended [15]. The latter protocol exceeds the manufacturer's guidelines for patients heavier than 17 kg. Neither recommendation is evidence based. Only two patients treated with 15 mg per kg per hour over a prolonged course have been well described in the literature [53,54]. Furthermore, continuous IV deferoxamine therapy in patients with acute iron poisoning for longer than 24 to 48 hours has been associated with the development of adult respiratory distress syndrome [55]. Four patients with mild-to-moderate iron poisoning without evidence of shock, acidosis, or sepsis who received 15 mg per kg per hour of deferoxamine intravenously for 2 to 3 days died of noncardiogenic pulmonary edema [55]. Continuous IV deferoxamine therapy should not routinely exceed the first 24 hours. If prolonged chelation therapy is deemed necessary, interrupting therapy for 12 of every 24 hours to allow excretion of ferrioxamine can be considered. Careful monitoring of pulmonary status is required during prolonged therapy.

Indications for discontinuing deferoxamine therapy include resolution of the signs and symptoms of systemic iron toxicity and correction of acidosis. Deferoxamine therapy is rarely needed beyond 24 hours and should be used with caution for periods longer than this.

Adverse drug events from short-term deferoxamine therapy are few, but significant. Rapid IV administration is associated with tachycardia, hypotension, shock, a generalized beet-red flushing of the skin, blotchy erythema, and urticaria. Acute renal failure can result when deferoxamine is administered to patients with hypovolemia [33]. Pulmonary toxicity and acute respiratory distress syndrome are associated with continuous IV therapy over several days [55]. Patients receiving deferoxamine may be at increased risk for *Yersinia* infections [27,38].

Before discharge, a psychiatric assessment is indicated for all patients with purposeful ingestions. Those who have required deferoxamine therapy should have a follow-up visit approximately 1 month after discharge. At this time, the patient's iron status and gastrointestinal tract should be assessed. He or she should also be advised of the symptoms of gastrointestinal obstruction and to return immediately if they occur. Chronic hepatic or cardiac dysfunction has not been reported after acute iron overdose.

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CHAPTER 137 ■ ISONIAZID POISONING

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Isoniazid (isonicotinic acid hydrazide [INH]) is the cornerstone of treatment and prevention of tuberculosis. It is available under a variety of brand names in 50-, 100-, and 300-mg tablets; as an oral syrup (50 mg per 5 mL); as an injectable solution (100 mg per mL); and in powder form. It is also available in combination with rifampin, pyridoxine, and other antitubercular drugs.

In 2007, the American Association of Poison Control Centers reported 330 cases with exposure to INH, including 228 single exposures [1]; 33% of the cases involved adults, with 34% being intentional. No deaths were reported, but 33% of the cases exhibited moderate-to-severe toxicity.

PHARMACOLOGY

As a bactericidal agent, INH interferes with lipid and nucleic acid biosynthesis in the growing *Mycobacterium* organism. It is rapidly and nearly completely absorbed after oral administration, with peak plasma concentrations occurring within 1 to 2 hours [2]. The rate and extent of absorption are decreased by food. The volume of distribution of INH approximates total body water (0.67 ± 0.15 L per kg), with cerebrospinal fluid concentrations 90% of those of serum [3]. INH passes into breast milk and through the placental barrier. There is little protein binding.

Between 75% and 95% of an INH dose is metabolized in the liver within 24 hours by acetylation to acetylisoniazid and hydrolysis to isonicotinic acid and hydrazine [2]. Genetic variation in its metabolism significantly alters plasma concentration, elimination half-life, and toxicity [4]. The elimination half-life in rapid acetylators (e.g., Asians, Eskimos, and American Indians) is 0.5 to 1.5 hours, whereas it is 2 to 4 hours in slow acetylators (e.g., people of African descent and Caucasians) [5]. The elimination half-life can be prolonged in people with liver disease. Rapid acetylators excrete 2.5% of INH as unchanged drug, compared with 10% in slow acetylators [2]. In addition, slow acetylators may have a higher percentage of the dose metabolized to hydrazine, a potential hepatotoxin [6]. INH exhibits dose-dependent inhibition of the mixed-function oxidases CYP2C19 and CYP3A, increasing the risk of adverse drug reactions in slow acetylators during the coadministration of drugs metabolized by these enzymes (e.g., phenytoin, carbamazepine, and diazepam) [7].

The usual adult INH dose is 5 mg per kg per day (maximum, 300 mg). The dose is increased to 15 mg per kg (maximum, 900 mg) when INH is used in combination with other antitubercular drugs and administered twice weekly. Acute ingestion of 1.5 to 3.0 g in adults may be toxic, with 6 to 10 g uniformly associated with severe toxicity and significant mortality [8]. The pediatric INH dose is 10 to 15 mg per kg per day (maximum, 300 mg) and is increased to 20 to 30 mg per kg (maximum, 900 mg) when concurrent INH and other antitubercular drugs are administered twice weekly. When INH is used in combination with rifampin, limiting the INH dose to 10 mg per kg per day and the rifampin dose to 15 mg per kg per day may minimize hepatotoxicity in children [9]. In patients with preexisting seizure disorders, convulsions have occurred with doses as low as 14 mg per kg per day; 19 mg per kg per day resulted in seizures in a 7-year-old child [8].

Daily therapeutic INH doses produce peak serum concentrations between 1 and 7 µg per mL. Intermittent INH therapy may produce concentrations between 16 and 32 µg per mL. Serum INH concentrations in acute ingestions have ranged from 20 µg per mL to more than 710 µg per mL, with little correlation to severity of intoxication [10–13].

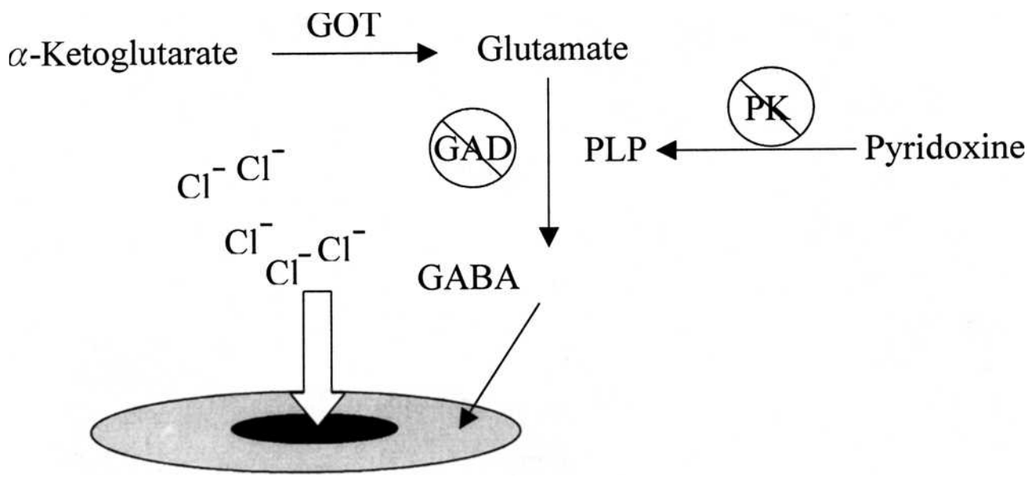

FIGURE 137.1. Role of isoniazid in the reduction of γ -aminobutyric acid (GABA) concentration. Cl^-, chloride ions; GAD, glutamic acid decarboxylase; GOT, glutamic oxaloacetic transaminase; PK, pyridoxine kinase; PLP, pyridoxal 5′-phosphate; ⊘, inhibited by isoniazid.

The central nervous system toxicity of INH and its metabolites is believed to be due to a decrease in the concentration of γ -aminobutyric acid, an inhibitory neurotransmitter that suppresses neuronal depolarization by opening chloride ionophores (Fig. 137.1). INH combines with pyridoxine (vitamin B_6) and is excreted in the urine as pyridoxal isonicotinylhydrazine [14]. It also competes with pyridoxine for pyridoxine kinase, the enzyme that converts pyridoxine to pyridoxal 5′-phosphate, the cofactor for glutamic acid decarboxylase–mediated conversion of glutamate to γ -aminobutyric acid [15]. In addition, INH inhibits glutamic acid decarboxylase activity. Its metabolism results in metabolites such as hydrazides and hydrazones, which inhibit pyridoxal 5′-phosphate and pyridoxine kinase, respectively [16].

INH causes a peripheral neuropathy that may be responsive to pyridoxine supplementation [17]. Wallerian degeneration of the myelin sheath and axon with blockade of fast axoplasmic transport is noted, with sensory nerves affected more than motor nerves [18–22]. Peripheral neuropathy is most commonly associated with chronic INH use in slow acetylators but may occur after acute massive overdose [23,24].

The mechanism of INH-induced hepatic injury is not understood. Hepatitis occurs in 0.1% to 1.1% of patients receiving INH, especially those with advanced age and alcohol consumption [25–28]. Concurrent rifampin therapy increases the incidence of hepatitis to 2.7% in adults and 6.9% in children [9,25–28]. It is unclear whether this effect is due to an influence of rifampin on INH metabolism or to the additive effect of two hepatotoxic drugs [28]. The histopathologic pattern of hepatic injury closely resembles viral hepatitis. Hypersensitivity seems unlikely, as rechallenge often fails to produce recurrence. Hepatic damage may be due to hydrazine metabolites of INH, covalently binding to liver macromolecules and producing necrosis [29]. Both rapid and slow acetylators have been described as having a greater risk for hepatotoxicity, although other researchers failed to find an association with acetylator status [26,30]. More recent work suggests that slow acetylators may be more susceptible to antitubercular drug–induced hepatitis and may develop more severe hepatotoxicity than do rapid acetylators [31].

The severe metabolic acidosis seen in acute INH intoxication is almost entirely due to seizure activity [32]. Although INH may interfere with nicotinamide adenine dinucleotide–mediated conversion of lactate to pyruvate, acidosis was not observed in animal studies until seizures occurred and lactic acidosis resolved within 2 hours after seizures ceased [32]. β-Hydroxybutyric acid production has also been reported after INH overdose, but does not appear responsible for INH-induced acidosis [33].

Hyperglycemia may result from disruptions of the Krebs cycle that require nicotinamide adenine dinucleotide and from stimulation of glucagon secretion [12].

CLINICAL PRESENTATION

Signs and symptoms usually appear within 30 minutes to 2 hours after acute INH overdose. Nausea, vomiting, dizziness, slurred speech, blurred vision, and visual hallucinations (e.g., bright colors, spots, and strange designs) are among the first manifestations [8,10]. Stupor and coma can develop rapidly, followed by intractable tonic–clonic generalized or localized seizures, hyperreflexia or areflexia, and cyanosis [8,10]. In severe cases, cardiovascular and respiratory collapse results in death. Oliguria progressing to anuria has been reported [8]. The metabolic alterations are striking and include severe metabolic acidosis, hyperglycemia, glycosuria, ketonuria, and hyperkalemia [8,10,12]. The triad of metabolic acidosis refractory to sodium bicarbonate therapy, seizures refractory to anticonvulsants, and coma suggests INH toxicity.

Hepatotoxicity usually presents as elevated serum aspartate aminotransferase values within the first few months of therapy. Fatalities from INH-induced hepatitis during chemoprophylaxis are between 4.2 and 7.0 per 100,000 persons [34]. When peripheral neuropathy occurs, it is within 3 to 35 weeks of initiating the therapy [22]. Other chronic effects include dysarthria, irritability, seizures, dysphoria, and inability to concentrate [25]. Optic neuritis and optic atrophy have also been reported, but their occurrence is often associated with the administration of ethambutol as well [35,36].

DIAGNOSTIC EVALUATION

Initial laboratory evaluation should include serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, and magnesium levels. Laboratory workup for anion-gap metabolic acidosis (e.g., serum methanol, ethylene glycol, salicylate, and acetaminophen levels) should also be considered. Arterial blood gases, electrocardiogram, chest radiograph, head computed tomography, and lumbar puncture should be obtained as clinically indicated.

Qualitative INH identification in urine using reagent-impregnated paper strips or a point-of-care testing device sensitive to INH metabolites [37,38] and quantitative serum INH identification are not widely enough available to be clinically useful to confirm diagnosis.

Acute INH intoxication should be considered in the differential diagnosis of any patient presenting with unexplained neurologic symptoms, particularly intractable seizure activity [8,13]. Conditions that may resemble INH toxicity include (a) central nervous system tumors and infections; (b) electrolyte abnormalities; (c) thyroid dysfunction; (d) hypoglycemia; (e) poisoning by anticholinergic, cholinergic, and sympathomimetic agents, or by tricyclic antidepressants (e.g., amoxapine), theophylline, organophosphates, meperidine (normeperidine), propoxyphene (norpropoxyphene), carbon monoxide, or cyanide; and (f) withdrawal syndromes [39]. Other causes of an anion-gap metabolic acidosis such as diabetic ketoacidosis, uremia, ethylene glycol, methanol, and salicylates should also be considered.

Ingestion of rifampin–INH combination products may produce, in addition to the symptoms of INH poisoning, (a) a striking red-orange discoloration of the skin, urine, sclera, and mucus membranes; (b) periorbital or facial edema; (c) pruritus; and (d) nausea, vomiting, or diffuse abdominal tenderness [40]. Transient elevations in total bilirubin and alkaline phosphatase, indicating cholestasis, may also be noted.

MANAGEMENT

The initial management of a patient with acute INH overdose focuses on protection of airway, support of respiration, treatment of seizures, correction of metabolic acidosis, minimization of drug absorption, and in selected cases, enhancement of INH elimination.

Gastrointestinal decontamination, if performed, should consist of the administration of activated charcoal. In severely ill patients, gastric lavage should be considered. Emesis is contraindicated because of the potential for rapid and unpredictable onset of seizures and coma.

Patients who have ingested a potentially toxic INH dose should be observed for at least 6 hours [8]; those who remain asymptomatic after gastrointestinal decontamination may be referred for psychiatric evaluation. All symptomatic patients should be admitted to an intensive care setting.

Seizures are often refractory to most conventional anticonvulsants [41]. Diazepam appears to be the most effective single agent, but its efficacy may be limited and large doses may be required. Animal data suggest sodium valproate may be effective [42]. Pyridoxine has dose-related effectiveness against convulsions and prevents lethality at doses from 75 to 300 mg per kg in canine models of INH toxicity [43]. In animal studies, when single-anticonvulsant regimens of pyridoxine, phenobarbital, pentobarbital, phenytoin, and diazepam were compared with the latter four anticonvulsants in combination with pyridoxine; pyridoxine was the only single agent that reduced the severity of convulsions and prevented death [41,43]. The combination of each of the other anticonvulsants with pyridoxine also prevented both convulsions and death. Therefore, pyridoxine, in conjunction with a benzodiazepine such as diazepam or lorazepam, is the preferred treatment for neurologic toxicity.

Intravenous pyridoxine therapy should be administered at the first sign of neurologic toxicity in milligram doses equal to the amount of INH ingested [8,10,44]. INH-overdosed patients treated with such pyridoxine doses exhibited no recurrent seizure activity, a decreased duration of coma, and prompt resolution of their metabolic acidosis [13]. If the amount of INH ingested is unknown, at least 5 g of pyridoxine should be administered [8,10]. In patients without seizures, the pyridoxine dose may be administered over 30 to 60 minutes. In those with seizure activity, it may be given as a bolus during 3 to 5 minutes. The pyridoxine dose should be repeated if seizures persist or recur. Intravenous diazepam or lorazepam should also be given [8,41]. As inadequate intravenous stores of pyridoxine in treating facilities have recently been documented, oral high-dose pyridoxine may be tried in the same doses as intravenous pyridoxine [45,46]. Seizures refractory to pyridoxine and diazepam have been successfully treated with thiopental-induced coma [47]. Reversal of prolonged INH-induced coma has been temporally associated with pyridoxine therapy [48].

Treatment of metabolic acidosis should be guided by arterial blood gas and electrolyte measurements. In most cases, intravenous sodium bicarbonate will not correct acid–base abnormalities until seizure activity is terminated [13]. Bicarbonate should be considered if the serum pH is lower than 7.2 or if the acidosis does not rapidly resolve after seizure control.

The role of forced diuresis in the management of INH overdose is unclear. Large amounts of INH recovered in the urine of some patients (43% to 58% of ingested doses) are offset by those reporting minimal recovery (6 to 144 mg) [11,49,50]. Peritoneal dialysis is somewhat effective but inefficient, whereas exchange transfusion is ineffective [49,51]. Hemodialysis and charcoal hemoperfusion increase the clearance of INH and decrease its half-life by 50%, but they have not been reported to remove significant quantities of INH (90 to 340 mg) [50,52].

Considering the rapid elimination half-life of INH and the efficacy of pyridoxine and benzodiazepine therapy, measures to enhance INH elimination are of limited use in the routine management of INH toxicity. However, patients with intractable acid–base disturbances, persistent seizures, or liver or renal dysfunction should be considered candidates for hemodialysis or charcoal hemoperfusion (if available). Unless the patient has experienced significant anoxia as a result of coma or seizures, neurologic recovery may be expected within 24 to 48 hours.

Prevention of peripheral neuropathy during chronic INH therapy can be accomplished by the administration of pyridoxine, 15 to 50 mg per day, in high-risk patients [19]. Peripheral neuropathy that develops during INH therapy is generally reversible on withdrawal of INH and treatment with high-dose pyridoxine (100 to 200 mg per day) [19]. However, the neuropathy may take months to a year or more to resolve, and in some cases, it may be permanent.

The management of INH-induced hepatotoxicity includes supportive care and cessation or reduction of INH administration. It is recommended that INH be discontinued in patients whose transaminase concentrations have risen to three times the upper limit of normal in the presence of jaundice or hepatitis symptoms or greater than five times the upper limit of normal if asymptomatic [27,30].

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CHAPTER 138 ■ LITHIUM POISONING

KENT R. OLSON AND THANJIRA JIRANANTAKAN

Lithium was introduced in the nineteenth century for the treatment of gout. Apparently, toxicity was rarely encountered because of low recommended doses. In the 1940s, lithium chloride was briefly marketed as a salt substitute, but was withdrawn after several cases of serious intoxication and death resulted from its use. In 1949, its antimanic properties were reported, and lithium has found increasingly wide psychiatric use since its approval by the U.S. Food and Drug Administration in 1970 [1,2].

In patients with mania, lithium reduces hyperactivity, irritability, pressured speech, assaultive behavior, and sleeplessness. These effects may require several days of therapy, during which time alternate medications are used. Lithium is very effective in reducing the recurrence of episodes of manic–depressive bipolar disorder and is used to treat some patients with unipolar depression and schizophrenia. It induces neutrophilia (up to 1.5 to 2.0 times the normal leukocyte counts) by enhanced production of G-CSF (granulocyte colony-stimulating factor) and stimulation of pluripotential stem cell production. Lithium has been used to treat a variety of causes of neutropenia [1,3,4].

Lithium is available in conventional tablets or capsules containing 300 mg (8.12 mEq) of lithium carbonate or in sustained-release preparations containing 450 mg (12.18 mEq) of lithium carbonate. Liquid solutions of lithium citrate containing 8 mEq per 5 mL are also available [3].

PHARMACOLOGY

Lithium is the lightest alkali metal, occupying the same column in the periodic table as sodium and potassium, elements with which it shares some properties. However, it has no known normal physiologic role. The exact mechanisms of its therapeutic and toxic effects remain to be determined. Lithium affects ion transport and cell membrane potential by competing

with sodium and potassium and possibly other cations. However, unlike sodium and potassium, lithium does not produce a large distribution gradient and, therefore, cannot maintain a significant membrane potential. It is believed to enhance serotonin and acetylcholine effects, resulting in an indirect effect on the central nervous system (CNS). In addition, its inhibitory effects on second messengers, such as inositol phosphates, may reduce neuronal responsiveness to some neurotransmitters [1].

Lithium is readily absorbed from the gastrointestinal tract. The bioavailability of conventional tablets and capsules and the liquid solution is 95% to 100%; bioavailability is not affected by food. Normally, absorption is complete within 1 to 6 hours; peak levels are reached in 2 to 4 hours [1,3]. Sustained-release preparations are less predictably absorbed (60% to 90%), and peak levels may be delayed by more than 4 to 12 hours [3]. Overdose has resulted in delayed peak levels or secondary peak levels as long as 148 hours after ingestion [5]. In one case, esophagoscopy at 84 hours revealed a 5- to 6-cm tablet and hair bezoar in the stomach [6].

Lithium initially occupies an apparent volume of distribution of 0.3 to 0.4 L per kg (approximately that of intracellular water), but further distribution into various intracellular tissue compartments occurs during 6 to 10 hours, with the final volume of distribution being 0.7 to 1.0 L per kg. This explains why initial serum lithium levels may be very high, with few or no signs of toxicity. After a single dose, the equilibrium serum lithium concentration can be expected to increase by 1.0 to 1.5 mEq per L for each 1.0 mEq of lithium per kilogram of body weight. Steady-state tissue levels are achieved after 3 to 4 days of the therapy. Tissue distribution is uneven; whereas the cerebrospinal fluid lithium concentration is only 40% to 60% that of plasma, the saliva concentration may be two to three times greater than that of plasma. Lithium is not bound to serum proteins and freely crosses the placenta [1,3].

Lithium is not metabolized. More than 95% of absorbed lithium is excreted by the kidneys, with 4% to 5% eliminated in sweat and 1% in the feces. It is also excreted in breast milk. Eighty percent of renally filtered lithium is reabsorbed in the proximal tubule against a concentration gradient that does not distinguish lithium from sodium. Sodium depletion can result in as much as a 50% increase in lithium reabsorption. The usual renal clearance is 10 to 40 mL per minute, but it may be 10 to 15 mL per minute or less in the elderly and in patients with renal dysfunction or dehydration [3,7,8]. However, lithium excretion rate may be different in different types of renal failure. Some study demonstrated increased fractional excretion of lithium in patients with prerenal failure, but decreased fractional excretion in acute tubular necrosis (ATN) renal failure [9]. The elimination half-life averages 20 to 24 hours; in patients with chronic intoxication, it may be as long as 47.6 hours [10]. The very slow terminal elimination phase may last up to 10 to 14 days because of gradual lithium release from tissue storage sites such as a bone and the brain [1].

Therapeutic serum lithium concentrations are usually considered to be 0.80 to 1.25 mEq per L; prophylaxis against recurrent manic–depressive illness may be achieved with levels of 0.75 to 1.00 mEq per L. Drug levels should be drawn at least 10 to 12 hours after the last dose to allow for complete tissue distribution. Onset of therapeutic effects usually requires 5 to 21 days after initiation of daily drug administration. Therapeutic levels are achieved by administration of 600 to 1,200 mg of lithium carbonate (16 to 32 mEq of lithium) per day. Careful monitoring of lithium levels is essential because of its low toxic-to-therapeutic ratio [3].

Lithium intoxication primarily involves the CNS and kidneys, although a variety of other organ systems are also affected (Table 138.1). Lithium intoxication may follow an acute overdose or result from chronic accumulation because of either an increase in dosage or a decrease in lithium elimination by the kidneys. Most serious toxicity occurs in patients with chronic intoxication, especially in older patients and patients with renal insufficiency [11].

TABLE 138.1

COMMON FEATURES OF LITHIUM INTOXICATION

Feature	Number	Percentage of total
Confusion	19[a]	68
Agitation	17	61
Drowsiness	16[a]	57
Mutism	5	18
Coma (grades III–IV)	1	4
Convulsions	4	14
Hyperreflexia	22	79
Increased tone	16	57
Ankle clonus	4	14
Extensor plantar responses	3	11
Tremor	18	64
Ataxia	14	50
Dysarthria	10	36
Myoclonus	7	25
Vomiting	7	25
Diarrhea	4	14
Acute diabetes insipidus	3	11
Acute renal failure	2	7

[a]Excludes one patient who also took temazepam in overdose.
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Acute ingestion of at least 1 mEq per kg (40 mg per kg of lithium carbonate) in a person not previously taking lithium would be required to produce a potentially toxic serum lithium level. The acute toxic dose in a patient already taking lithium ("acute-on-chronic" overdose) depends on the prior lithium level (due to tissue soaking). The dose required to produce chronic intoxication depends on the individual's rate of renal elimination of lithium.

CLINICAL MANIFESTATIONS

Signs and symptoms of mild lithium intoxication include nausea, vomiting, lethargy, fatigue, memory impairment, and fine tremor. Moderate signs and symptoms of toxicity include confusion, agitation, delirium, coarse tremor, hyperreflexia, hypertension, tachycardia, dysarthria, nystagmus, ataxia, muscle fasciculations, extrapyramidal syndromes, and choreoathetoid movements. Patients with severe toxicity may also exhibit bradycardia, complete heart block, Brugada syndrome, coma, seizures, nonconvulsive status epilepticus, hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, and hypotension [12–15]. Permanent sequelae include choreoathetosis, tardive dystonia, tremor, peripheral neuropathy, scanning speech, dysarthria, muscle rigidity, cognitive deficits, nystagmus, and ataxia [16–20].

Neurotoxic effects of lithium usually develop gradually and may become progressively severe over several days. Neurologic manifestations may worsen even as serum lithium levels are falling and may persist for days to weeks after cessation of the therapy, in part because of slow movement of lithium into and out of intracellular brain sites and possibly brain damage, such as demyelination caused by lithium [19].

Cardiovascular manifestations are nonspecific. The electrocardiogram changes are often similar to those seen with hypokalemia and may result from displacement of intracellular

potassium by lithium; U waves and flattened, biphasic, or inverted T waves can be seen with therapeutic doses and mild overdoses. Sinus and junctional bradycardia, sinoatrial and first- degree AV block, and QRS and QTc interval prolongation may be seen with severe intoxication [20,21]. Life-threatening dysrhythmias are rare. Patients with complete heart block during lithium treatment have been reported [12,13]. This lithium-associated cardiac toxicity is more common in patients older than 65 years with baseline EKG abnormalities, conduction abnormalities, use of renal toxic medication, and concomitant use of AV nodal–blocking agents [13]. Brugada syndrome precipitated by lithium has been reported [14]. Pulse and blood pressure abnormalities may be seen in moderate or severe poisoning, but they are usually not pronounced. Hypotension is more often due to dehydration, which can be a cause and a complication of lithium intoxication, than direct cardiotoxicity [20,21].

Chronic lithium therapy has several important effects on renal function, including impaired urinary concentrating ability, nephrogenic diabetes insipidus (NDI), and a sodium-losing nephritis [2]. These effects appear to be dose related and usually correct within several weeks of discontinuing the therapy [20]. Excessive water and sodium loss lead to increased proximal tubular reabsorption of lithium by transport mechanisms designed for sodium reabsorption. The accumulation of lithium may be enhanced by illnesses that result in decreased glomerular filtration rate, such as fever with sweating, gastroenteritis, and heart failure, or by diuretic drugs that enhance distal tubular sodium and fluid loss. Rising lithium levels may further aggravate nephrotoxicity. A patient who has remained stable with a satisfactory lithium serum level at a constant daily dosage for years may suddenly develop life-threatening intoxication within days of entering such a vicious cycle [2].

Metabolic abnormalities associated with lithium use include hypercalcemia, hypermagnesemia, nonketotic hyperglycemia, transient diabetic ketoacidosis, and goiter. Hypothyroidism is rare [20].

Lithium is teratogenic in rats, mice, and rabbits, and human fetal malformations have been described, including cardiac defects such as Ebstein's anomaly [22].

Several drugs may interact with lithium to alter its pharmacokinetics or directly enhance its toxicity. Diuretics may promote fluid and sodium depletion, leading to enhanced tubular lithium reabsorption. This effect appears to be much less apparent with furosemide than with thiazide diuretics. Aminophylline, urea, bicarbonate, and acetazolamide may decrease serum lithium levels by increasing the glomerular filtration rate. Nonsteroidal anti-inflammatory drugs, including the selective cyclooxygenase-2 inhibitor rofecoxib [23], may decrease the glomerular filtration rate and lithium elimination. Antipsychotic medications may have additive CNS depressant effects; in addition, lithium may enhance their dopamine-blocking and serotonergic effects and induce or aggravate rigidity and hyperthermia, possibly inducing neuroleptic malignant syndrome and serotonin syndrome [15,20]. Angiotensin-converting enzyme inhibitors (ACEIs) increase steady-state lithium concentrations by 36.1% and reduced lithium clearance by 25.5% resulting patients presented with lithium toxicity [24].

DIAGNOSTIC EVALUATION

The history should include the type of lithium preparation ingested, the amount(s) and time(s) of ingestion, and the nature of the symptoms. It is important to differentiate patients with acute lithium overdose from those with chronic intoxication resulting from excessive daily doses or impaired renal elimination.

The physical examination should focus on the vital signs, neurologic function, and cardiovascular status. All patients should have an electrocardiogram and laboratory evaluation, including serum electrolytes, glucose, blood urea nitrogen, creatinine, and serum lithium level. Lithium levels should be repeated at frequent (i.e., 2- to 4-hour) intervals after acute overdose until peak levels are observed. If the levels are elevated, they should be repeated until they fall below the toxic range and the patient becomes asymptomatic. Electroencephalography should be considered in patients who presented with coma to evaluate nonconvulsive status epilepticus [15].

Patients with chronic intoxication are typically brought to medical attention by a family member or therapist because of neurologic symptoms. There is usually a recent history of excessive fluid loss caused by gastroenteritis, other flulike illness, or excessive urination. The severity of chronic intoxication generally correlates with the serum lithium level [2,20]. In patients undergoing chronic therapy, mild neurotoxic effects may occur with serum lithium concentrations of less than 1.5 mEq per L. Steady-state concentrations of 1.5 to 3.0 mEq per L are associated with mild or moderate toxicity. Severe poisoning and death may occur with serum concentrations greater than 3 to 4 mEq per L [2,10,20].

After acute overdose, the predominant initial symptoms are nausea and vomiting [2]. Patients do not usually have significant neurologic manifestations despite high serum lithium levels during the first 12 hours or more after ingestion because lithium is taken up slowly by the brain and other tissues [10]. Serum lithium concentrations as high as 10.6 mEq per L without significant toxicity have been reported after acute overdose [25–27]. However, intoxication may develop during the subsequent 24 to 48 hours, even as serum levels fall [19,20,28]. Levels drawn shortly after acute or acute-on-chronic overdose cannot be used reliably to predict toxicity or guide therapy (Fig. 138.1) [2,10]. There does not appear to be any clinical variable that accurately predicts which patients will deteriorate. The use of cerebrospinal fluid levels to estimate brain concentrations more closely has been advocated [29]. However, cerebrospinal fluid concentrations do not reflect intracellular brain tissue levels or predict the level of coma (Fig. 138.2) [2,25,30].

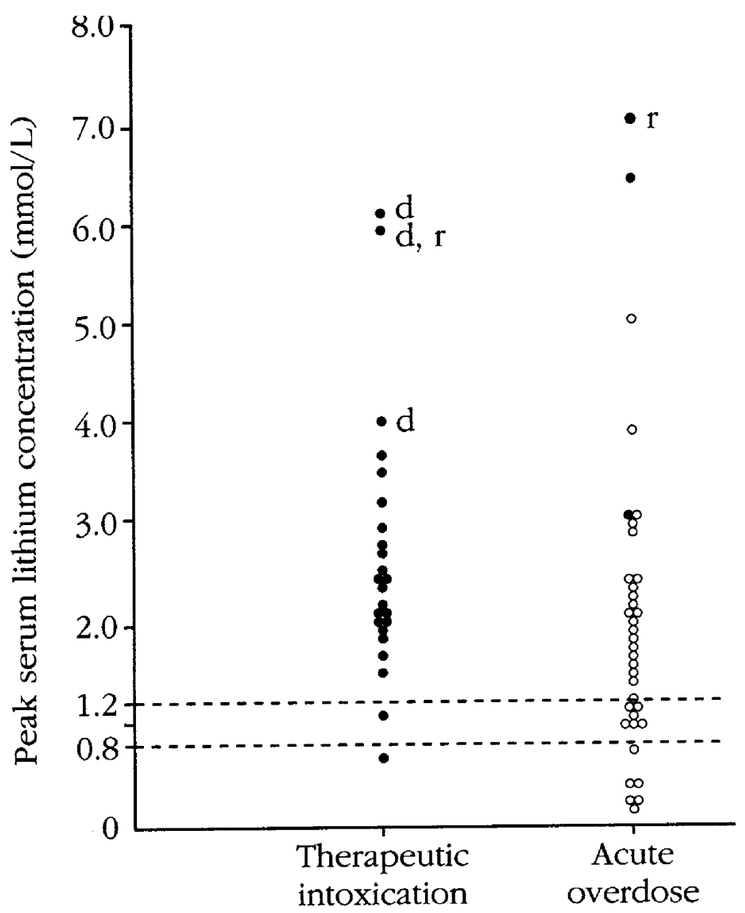

FIGURE 138.1. Lack of correlation between serum levels and toxic manifestations in patients with acute intoxication. d, diabetes insipidus; r, renal failure. [Reprinted from Dyson EH, Simpson D, Prescott LF, et al: Self-poisoning and therapeutic intoxication with lithium. *Hum Toxicol* 6:326, 1987, with permission.]

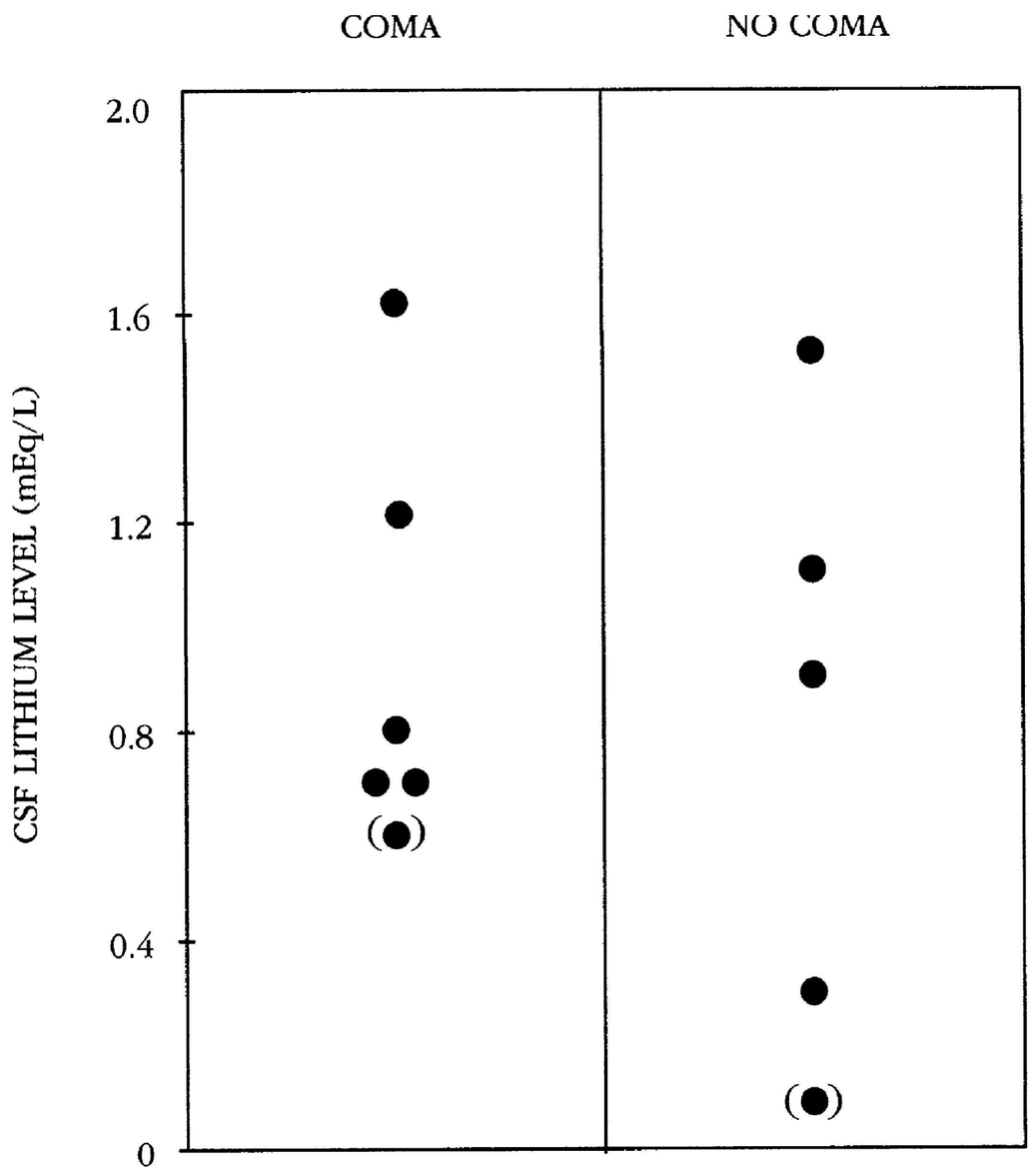

FIGURE 138.2. Cerebrospinal fluid (CSF) levels in patients with and without coma. [Reprinted from Lee BL, Brown CR, Becker CE, et al: Lithium overdose: factors that predict outcome in poisoned patients. *Vet Hum Toxicol* 28:505, 1986, with permission.]

Patients with acute-on-chronic overdose usually have a clinical course similar to those with acute ingestions. However, a smaller total dose may produce severe intoxication, depending on the preingestion therapeutic serum level.

Elevated blood urea nitrogen and creatinine reflect renal insufficiency and suggest that intoxication results from gradual accumulation of lithium rather than acute ingestion. Elevated creatinine may also be caused by cross-reactivity of the assay with creatine from muscle destruction and should prompt the measurement of serum creatine phosphokinase and urinalysis for myoglobinuria.

Patients with lithium-induced NDI usually have dilute urine with a low-measured osmolality relative to serum. The diagnosis is confirmed by lack of response to administered vasopressin by the inappropriately dilute urine [16].

Leukocytosis may be seen in patients taking lithium. It is a nonspecific finding and does not reflect severity of intoxication. A reduced or absent anion gap may occur with severe lithium carbonate intoxication [31], probably because the carbonate anion (but not the lithium cation) is measured and used in calculating the anion gap [32].

Plain radiographs of the abdomen may or may not reveal radiopaque lithium tablets after acute ingestion. A negative radiograph should not be used to rule out acute ingestion [33].

Conditions such as hypoxia, hypoglycemia, hypothermia or hyperthermia, electrolyte disturbances, CNS infection, head trauma, and intracranial bleeding should be included in the differential diagnosis of patients with lithium poisoning. In a patient with hyperthermia and rigidity who is also taking antipsychotic medications, neuroleptic malignant syndrome and serotonin syndrome should be considered (see Chapter 68). Other drug intoxications should be considered (see Chapter 68), especially if CNS symptoms appear shortly after an acute overdose.

MANAGEMENT

In patients with altered mental status, initial management should include (a) assessment and stabilization of the airway; (b) administration of oxygen; (c) assisted ventilation, if needed; (d) vascular access; and (e) administration of dextrose, naloxone, and thiamine. Diazepam or barbiturates should be administered to patients with seizures. Patient with nonconvulsive status epilepticus should be monitored by electroencephalography to confirm the resolution of seizure activity. If hyperthermia is present, immediate cooling measures should be instituted, including tepid sponging and fanning and neuromuscular paralysis, if needed. Hypovolemia, if present, should be treated with intravenous crystalloids. Cardiac dysrhythmias do not usually require treatment, but should respond to usual agents.

Asymptomatic patients with acute or acute-on-chronic overdose should be observed for a minimum of 6 hours after ingestion. Serial lithium levels should be obtained to confirm lack of significant absorption. Patients with mild overdoses can often be monitored and treated in the emergency department. Symptomatic patients, patients with a massive acute ingestion, and those whose levels continue to rise beyond 6 hours after ingestion should be admitted to an intensive care setting.

Lithium-induced NDI does not respond to vasopressin, but it has been reported to improve with hydrochlorothiazide, amiloride, carbamazepine, and indomethacin [20]. However, the gradual onset and the duration required of hydrochlorothiazide, carbamazepine, and amiloride therapy would limit their clinical usefulness. One case report suggests indomethacin may be acutely effective in treating lithium-induced NDI [34].

After acute ingestion, the gastrointestinal tract should be decontaminated as soon as possible to prevent continued absorption of lithium. Ipecac-induced emesis is not recommended because it yields poor return of gastric contents [35]. Gastric lavage can be performed, although there is little evidence for benefit [36]. Activated charcoal does not effectively bind lithium and should be given only if coingestion of another drug is suspected [37]. Whole-bowel irrigation (see Chapter 117) has been successful for large ingestions, especially if they involve sustained-release tablets [38]. If a tablet mass or concretion is suspected because of sustained high levels after 2 to 3 days, radiographic contrast studies, ultrasound, or gastroduodenal endoscopy and endoscopic removal should be considered [6]. Preliminary evidence in animals and human volunteers suggests that sodium polystyrene sulfonate (Kayexalate) binds lithium and may enhance its elimination [39,40]. One case report describes its use in a patient with acute-on-chronic lithium overdose [41]. There is no consensus at this point as to whether the administration of potassium with the polystyrene sulfonate enhances or decreases lithium excretion.

In most patients with mild or moderate intoxication, intravenous fluid therapy is effective in restoring and maintaining renal elimination of lithium. A crystalloid solution (half-normal or normal saline) aiming for urine output of 1 to 3 mL per kg per hour should be administered after an initial saline bolus (10 to 20 mL per kg), depending on the degree of dehydration. Serum electrolytes should be followed closely because hypernatremia may occur. To estimate the effectiveness of renal elimination, the lithium clearance can be estimated by obtaining simultaneous urine and serum lithium levels [42]:

Approximate renal lithium clearance = urine flow rate (mL/min) × urine lithium (mEq/L) / serum lithium (mEq/L).

Normal lithium clearance is 10 to 40 mL per minute. If the clearance is below normal in a patient without underlying cardiac or renal dysfunction, the rate of fluid administration should be increased because this suggests low renal perfusion secondary to dehydration. In human studies, water loading,

furosemide, thiazide, ethacrynic acid, ammonium chloride, and spironolactone did not increase lithium clearance. Sodium bicarbonate, acetazolamide, urea, and aminophylline were effective. However, clinical studies in patients with lithium intoxication treated by these agents have not been reported [7].

Hemodialysis is the most efficient method for removing lithium, achieving clearance rates of up to 100 to 150 mL per minute [2,30,42]. However, lithium is only slowly removed from intracellular tissue compartments, especially the brain, and rebound increases of serum lithium levels often occur within several hours after dialysis. Hemodialysis should be repeated frequently until the serum level drawn 6 to 8 hours after the last dialysis is 1 mEq per L or less [2]. However, despite repeated dialyses, patients with significant neurologic toxicity do not promptly improve. Recovery, if it occurs, may take several days to weeks [2,29,30].

The indications for hemodialysis are not well established. It is generally agreed that patients with severe clinical toxicity and those with renal dysfunction should undergo dialysis. Asymptomatic patients or those with mild-to-moderate intoxication who are otherwise healthy may be managed with intravenous fluids as long as they remain clinically stable or are improving and satisfactory lithium clearance (> 15 to 20 mL per minute) is achieved. Patients with chronic serum levels exceeding 2.5 mEq per L accompanied by symptoms and those with acute poisoning and peak levels exceeding 10 mEq per L (in which significant toxicity is expected to occur with subsequent tissue distribution) should also be considered for hemodialysis. However, some clinicians advocate hemodialysis for patients who have acute ingestion without prior lithium body burden and a serum lithium concentration greater than 4 mEq per L [43].

Continuous renal replacement therapy (e.g., venovenous or arteriovenous hemodiafiltration) has been reported to successfully remove lithium without the need for hemodialysis [44–47]. In one case, 14 hours of continuous arteriovenous hemodiafiltration was estimated to achieve lithium elimination equivalent to 5.75 hours of hemodialysis [48]. In another case report, clearances of up to 38 mL per minute were achieved with continuous venovenous hemodiafiltration [46]. Continuous renal replacement therapy removes lithium slowly, without rebound rises in levels seen with intermittent hemodialysis, and can also be performed in facilities without full dialysis capabilities.

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CHAPTER 139 ■ METHYLXANTHINE POISONING

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The methylxanthines most commonly used in the clinical setting are theophylline and its ethylenediamine salt, aminophylline. Until recently, theophylline was used exclusively as a bronchodilator for the management of reversible obstructive pulmonary diseases and as a respiratory stimulant for the treatment of apnea of prematurity in neonates. During the 1980s, its use fell dramatically as more effective therapies for recurrent bronchospasm became available [1]. However, there has been renewed interest in theophylline as the scope of its pharmacologic benefits broadens. Potential uses for theophylline now include preconditioning of cardiac ischemia [2], treatment of bradycardia [3], amelioration of perinatal asphyxia [4], acute mountain sickness [5], bradycardia after spinal cord injury [6], protection from contrast-induced nephropathy [7], and treatment of attention-deficit hyperactivity disorder [8]. Recent clinical trials of theophylline for asthma have demonstrated substantial benefit, restoring interest in the drug for this indication [9–16]. Despite its renewed popularity, theophylline, with its potent pharmacologic actions, variable metabolic disposition in humans, and narrow therapeutic-to-toxic ratio, is a common cause of intoxication [1,17].

Caffeine and theobromine are other widely used methylxanthines. Caffeine is found in many pharmaceutical preparations (e.g., antisleep drugs), as well as in dietary supplements, including guarana and kola nut. Although severe toxicity from caffeine ingestion is uncommon, case reports of serious poisoning in children and adults are well documented [18–20]. Because caffeine and other xanthine derivatives are structurally similar to theophylline, signs and symptoms of toxicity resemble those seen in theophylline intoxication, and the approach to management is identical.

Three clinical circumstances account for most cases of theophylline poisoning: unintentional ingestions by children, intentional ingestions (suicide attempts) by adolescents or adults, and medication errors (miscalculation of dose, change in frequency of administration, lack of serum drug level monitoring, or an unrecognized drug–drug or drug–disease interaction) [1,21,22]. Most cases of theophylline intoxication result from chronic, unintentional overmedication.

PHARMACOLOGY

Theophylline is available commercially as a liquid, tablet, sustained-release capsule, or solution for intravenous administration. Overdose of sustained-release theophylline can lead to a marked delay in complete absorption, with peak serum theophylline concentrations occurring as long as 15 to 24 hours after ingestion [23]. Therapeutic serum theophylline concentrations range from 10 to 20 µg per mL.

A loading dose of 5 to 6 mg per kg of intravenous aminophylline should produce a serum theophylline level of 10 µg per mL in patients not currently taking theophylline. Maintenance dosages vary with age and underlying conditions (Table 139.1). For patients taking theophylline regularly, a loading dose increases the steady-state serum theophylline level. Typically, administration of 1 mg per kg of theophylline raises the serum drug concentration by 2 µg per mL. This relationship can also be used to predict the theophylline concentration after an overdose; the maximum possible drug concentration (in micrograms per milliliter) should be no more than twice the ingested or administered dose (in milligrams per kilogram).

Theophylline has a volume of distribution of 0.4 L per kg and is 40% to 65% bound to plasma proteins [24]. Its metabolism is almost exclusively by hepatic cytochrome P450 system; it is oxidized or demethylated in the liver by at least two isoenzymes (CYP1A2 and CYP3A4) [24]. Less than 15% of the drug is excreted unchanged in urine. At therapeutic doses, hepatic metabolism generally occurs by first-order elimination kinetics [25]. The drug exhibits saturable (Michaelis–Menten) kinetics in overdose leading to prolonged, unpredictable elimination rates. The elimination half-life of theophylline also varies widely with age: typical half-lives are 20 to 30 hours in

TABLE 139.1

INTRAVENOUS AMINOPHYLLINE MAINTENANCE DOSES

Age group	Infusion rate (mg/kg/h)
Newborn	0.3–0.4
1–6 mo	0.5–0.6
6 mo–9 y	1.0–1.2
9–16 y	0.9–1.1
Smoker age 12–50 y	1.0
Nonsmoker age 16–50 y	0.5–0.7
Older than 50 y	0.4–0.6
Cor pulmonale	0.3–0.5
Liver failure	0.1–0.5
Congestive heart failure	0.1–0.5

† Deceased.

TABLE 139.2

FACTORS AFFECTING SERUM THEOPHYLLINE CONCENTRATIONS

Drugs that *increase* theophylline clearance
- Barbiturates
- Carbamazepine
- Cigarette smoke
- Phenytoin
- Rifampin

Drugs that *decrease* theophylline clearance
- Cimetidine
- Ciprofloxacin
- Clarithromycin
- Fluvoxamine
- Erythromycin
- Norfloxacin
- Ofloxacin
- Zafirlukast

Conditions that *increase* theophylline clearance
- Cigarette smoking
- Cystic fibrosis
- Hyperthyroidism

Conditions that *decrease* theophylline clearance
- Hepatitis/cirrhosis
- Congestive heart failure
- Some viral infections

TABLE 139.3

PHYSIOLOGIC EFFECTS OF THEOPHYLLINE

Central nervous system
- Stimulation of cortical centers
- Stimulation of medullary respiratory center
- Nausea and emesis
- Cerebral vasoconstriction and decreased cerebral blood flow

Cardiovascular
- Positive inotropic and chronotropic effects
- Vascular smooth muscle relaxation

Pulmonary
- Bronchial smooth muscle relaxation
- Increased ventilation
- Stimulation of diaphragmatic and intercostal muscles

Gastrointestinal
- Increased gastric acid and pepsin secretion
- Relaxation of esophageal smooth muscle and possible reflux

Renal
- Increased blood flow and glomerular filtration rate
- Increased diuresis (< 48 h)

Endocrine
- Increased plasma catecholamines
- Augmented dopamine β-hydroxylase and rennin

Metabolic
- Lipolysis
- Gluconeogenesis and glycogenolysis

Musculoskeletal
- Augmented contractility
- Disturbances in depolarization (e.g., tremor)

premature infants, 4 to 7 hours in newborns, 3 to 4 hours in children 6 months to 18 years of age, and 8 to 9 hours in adults [24–27]. Many drugs, chemicals, and medical conditions affect the steady-state serum concentration and elimination half-life of theophylline (Table 139.2). The drugs that inhibit theophylline clearance are those that inhibit CYP1A2 and CYP3A4, including erythromycin, clarithromycin, ciprofloxacin, and cimetidine [24,28]. Drugs that increase theophylline clearance include barbiturates, carbamazepine, and the polyaromatic hydrocarbons of cigarette smoke (including passive smoke inhalation) [29,30]. Enzyme induction by these drugs can be temporary; if patients who smoke quit abruptly, theophylline clearance can fall to normal within days, leading to inadvertent theophylline intoxication unless dose is adjusted accordingly. Several disease states are also associated with a reduction in theophylline clearance, including congestive heart failure and liver disease [24,31]. Both hyperthyroidism and cystic fibrosis are associated with increased elimination of theophylline [32].

Theophylline has a variety of physiologic effects in therapeutic doses (Table 139.3). These effects include smooth muscle relaxation, mild central nervous system (CNS) excitation, and diuresis. Intoxication is associated with an array of other metabolic and clinical consequences. Although the effects of theophylline have been well characterized, their pharmacologic and pathophysiologic mechanisms remain poorly understood. Three primary cellular mechanisms of theophylline action have been theorized: inhibition of cyclic guanosine monophosphate or cyclic adenosine monophosphate (cAMP) activity, adenosine receptor antagonism, and adrenergic hyperstimulation (particularly at the beta-receptor) secondary to elevated levels of circulating plasma catecholamines [33–36]. Inhibition of calcium translocation and leukotriene production has also been postulated to be a fourth mechanism.

The physiologic changes seen with therapeutic doses of theophylline, including tachycardia, diuresis, bronchodilation, and CNS excitation, were thought to result from theophylline's inhibition of phosphodiesterase, the intracellular enzyme that inactivates cAMP, an important "second messenger" [37]. Such enzyme inhibition would lead to elevated intracellular cAMP concentrations, affecting a broad range of physiologic responses. However, this theory has been brought into question; in vitro data indicate that phosphodiesterase inhibition does not occur at therapeutic serum concentrations of theophylline, suggesting that increased cAMP activity is not a major mechanism of its therapeutic effects [38]. Whether the increased theophylline concentrations seen in the intoxicated patient are sufficient to inhibit phosphodiesterase activity is unknown.

Investigation has also been directed at the role of adenosine receptor antagonism as a mechanism of theophylline action. Adenosine is a nucleoside that promotes smooth muscle constriction, slows cardiac conduction, and acts as an endogenous anticonvulsant. With the structure of theophylline being similar to that of adenosine and with the drug having opposite physiologic actions, theophylline may be a simple competitive antagonist at bronchial and vascular smooth muscle, cardiac, and CNS sites. However, adenosine antagonism alone does not provide a complete explanation for theophylline's pharmacologic effects [39,40].

Additional data suggest that many of theophylline's actions can be accounted for by its stimulation of plasma catecholamines release [32,41]. Plasma concentrations of epinephrine, norepinephrine, and dopamine all rise significantly after theophylline administration [40]. With therapeutic doses, plasma catecholamine activity typically increases four- to sixfold. After theophylline intoxication, plasma catecholamine activity may rise to 30-fold [33,35]. Increased plasma catecholamines provide a ready explanation for many of the effects of theophylline seen after therapeutic doses and

potentially mediate many of the effects of theophylline intoxication. In all probability, the combined effects of adenosine receptor antagonism and catecholamine release are responsible for the predominant effects of theophylline intoxication.

Plasma catecholamines, particularly epinephrine, are capable of inducing hypokalemia, hyperglycemia, and metabolic acidosis. Epinephrine-induced hypokalemia appears to result from β_2-adrenergic receptor–linked stimulation of Na^+/K^+ adenosine triphosphatase. This leads to increased intracellular transport of potassium with preservation of total body potassium content [42]. Consistent with the theories of plasma catecholamine activity is the observation that theophylline-induced hypokalemia can be inhibited by pretreatment with propranolol or reversed by propranolol administration [43].

The CNS effects of theophylline intoxication include respiratory stimulation, vomiting, and seizures. These may result from disturbances in CNS cyclic guanosine monophosphate activity, adenosine antagonism, or adrenergic excess. Changes in neuronal transmembrane potentials by any of these mechanisms would lower excitation thresholds. Additionally, there are theories that theophylline inhibits CNS γ-aminobutyric acid receptor activity and stimulates *N*-methyl-d-aspartate and other excitatory neurotransmitters production. Theophylline administration has been associated with an abnormal electroencephalogram pattern in 34% of children and 12% of adults [44,45]. Cerebral vascular effects are also significant with theophylline and other methylxanthines because they are potent cerebral vasoconstrictors. This is the presumed mechanism of the efficacy of caffeine in the treatment of migraine headache. However, decreases in cerebral blood flow can be extreme, particularly during inhalational anesthetics administration [46]. In animal models, theophylline amplifies brain damage induced by seizures [47].

CLINICAL TOXICITY

Manifestations of theophylline intoxication can be classified into five categories: cardiac, CNS, gastrointestinal, musculoskeletal, and metabolic [1,17]. The cardiovascular effects of theophylline intoxication consist of rhythm and vascular disturbances. The hallmark (and first sign) of theophylline poisoning is sinus tachycardia, which occurs in more than 95% of cases. With more severe intoxication, unstable supraventricular tachydysrhythmias and ventricular dysrhythmias may occur. A common cause of death with severe theophylline intoxication is intractable ventricular dysrhythmias.

Blood pressure disturbances are also common. At lower ranges of intoxication, a mildly elevated blood pressure may be present, although severe hypertension is unusual in isolated theophylline poisoning. In severe cases of theophylline poisoning, hypotension with a widened pulse pressure is seen in the face of an increased cardiac index. Hypotension is caused by a marked fall in systemic vascular resistance [34].

The CNS effects of theophylline poisoning become prominent in severe overdose. The stimulatory actions of theophylline first produce hyperventilation with mild respiratory alkalosis. Significantly intoxicated patients develop agitation and anxiety. Vomiting, which can be severe, partly results from stimulation of the vomiting center of the medullary chemoreceptor trigger zone.

The most severe CNS manifestation of theophylline intoxication is seizures; these are a poor prognostic sign. Theophylline-induced seizures are typically tonic–clinic in nature and may be focal; they may be single, but are commonly multiple and typically resistant to conventional anticonvulsants. Seizures after theophylline intoxication are associated with a high frequency of adverse neurologic outcomes and a mortality that approaches 50% in elderly patients [48,49].

The gastrointestinal effects of theophylline poisoning consist of vomiting, diarrhea, and hematemesis. Vomiting results in part from hypersecretion of gastric acid and the enzymes gastrin and pepsin [50]. These acids and digestive enzymes are gastric irritants that can produce mucosal hemorrhage with hematemesis. Finally, theophylline is a potent relaxer of lower esophageal sphincter resting tone; this action facilitates the reflux of gastric contents.

Skeletal muscle tremor is a common feature of theophylline poisoning. These tremors are coarse; myoclonic jerks may also be present. Muscular hypertonicity also appears to be linked to theophylline's actions as a β_2-adrenoreceptor; this is evidenced by a similar syndrome occurring after excess administration of potent β_2-agonists (e.g., terbutaline).

A number of metabolic disturbances accompany theophylline intoxication: metabolic acidosis, hypokalemia, hyperglycemia, hypophosphatemia, hypomagnesemia, and hypercalcemia [26,51–55]. The resulting clinical picture can mimic diabetic ketoacidosis [56]. Metabolic acidosis may appear late and is typically modest; acidemia may not occur because of a superimposed respiratory alkalosis. Hypokalemia and hyperglycemia correlate strongly with the degree of intoxication after acute theophylline poisoning [57]. However, there are no obvious clinical consequences of hypokalemia. Hypercalcemia and hypophosphatemia are common, but not invariable, disturbances. Their cause is unclear, although theophylline (and epinephrine) has been shown to increase concentrations of parathyroid hormone, and correction of theophylline-induced hypercalcemia has been reported after propranolol administration [58].

Several studies have suggested that the metabolic and clinical consequences of theophylline intoxication vary, depending on whether the poisoning occurs through a single ingestion (or single intravenous overdose), chronic overmedication, or acute-on-therapeutic intoxication, in which the patient has maintained serum theophylline concentrations in the therapeutic range but then received a single toxic dose [18,22]. With *acute theophylline intoxication*, the patient ingests a single toxic dose of theophylline or inadvertently receives a toxic dose of intravenous aminophylline. The clinical course of acute theophylline intoxication strongly correlates with serum theophylline concentration. Serum theophylline concentrations of 20 to 40 µg per mL are associated with nausea, vomiting, and tachycardia. When theophylline concentrations are 40 to 70 µg per mL, premature ventricular contractions, agitation, and tremor appear. At theophylline concentrations greater than 80 µg per mL, life-threatening events, including severe cardiac dysrhythmias and intractable seizures, occur [16,59,60]. Hypokalemia can be profound after acute intoxication, with serum potassium concentrations falling to as low as 2.1 mEq per L. Serum glucose can be as high as 300 to 350 mg per dL.

In *chronic theophylline overmedication*, the patient ingests theophylline for at least 24 hours in doses or under conditions that exceed theophylline clearance. The result is a relatively slow rise in body "theophylline burden"-to-toxic concentrations. Victims of chronic overmedication are more likely to be neonates or elderly patients who have underlying cardiac disease or are taking/receiving medications that inhibit theophylline metabolism. These factors contribute to greater morbidity and mortality after chronic theophylline overmedication [18,30]. Signs of severe intoxication may occur with steady-state serum theophylline concentrations as low as 20 to 30 µg per mL. Seizures have occurred in patients with concentrations as low as 17 µg per mL. Patients with chronic theophylline overmedication are also less likely to have hypokalemia and hyperglycemia. The most striking feature of chronic theophylline overmedication is that there is *no significant correlation* between serum theophylline concentration and the appearance of life-threatening events [1,22,61,62]. Seizures and

dysrhythmias may appear with serum theophylline concentrations in the therapeutic or mildly toxic range [22,61]. As a result, serum theophylline concentration *should not be used* to predict the appearance of these events.

Patients who are chronically receiving theophylline in appropriate doses and then take or receive an acute overdose of theophylline develop *acute-on-therapeutic theophylline intoxication*. In these patients, clinical and metabolic consequences have features that are intermediate between those found with acute intoxication and chronic overmedication. Clinical manifestations are somewhat predicted by peak serum theophylline concentration, with life-threatening events usually not appearing until serum theophylline concentrations exceed 60 µg per mL. Metabolic disturbances are not as severe and have little or no correlation with serum theophylline concentration [1,21,22].

Patient age appears to be a significant risk factor for the development of life-threatening events after theophylline intoxication with those at extremes of age (i.e., neonates and elderly patients) [1,62]. For example, after chronic overmedication, patients older than 75 years have an almost 10-fold greater risk of a life-threatening event than do adolescents with comparable serum theophylline concentration [1,62]. There is evidence that in patients with chronic theophylline intoxication, age is a better predictor of major toxicity than serum theophylline concentration. Potential explanations for this observation include the differing pharmacokinetics found at extremes of age or the higher prevalence of significant underlying multisystem disease and use of multiple drugs in these patients.

DIAGNOSTIC EVALUATION

Essential laboratory studies to obtain in the patient with theophylline intoxication include serum theophylline concentration, serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, liver function panel, and creatinine phosphokinase. Urine should be frequently evaluated for evidence of myoglobinuria. An electrocardiogram should be obtained; all patients with theophylline intoxication should be placed on continuous electrocardiogram monitoring. Arterial blood gas and complete blood cell count should be obtained as clinically indicated.

Sequential serum theophylline concentrations should be obtained every 1 to 2 hours until a plateau and subsequent substantive decline have been documented because delayed peaks in serum theophylline concentration may occur after an overdose. All abnormal laboratory studies should be serially monitored until all values have returned to normal.

MANAGEMENT

The management of theophylline intoxication consists of stabilization, decreasing absorption, and enhancing elimination. After acute ingestion, decreasing absorption is a primary concern. Treatment of chronic intoxication or intoxication after intravenous administration of theophylline generally focuses more on enhancing elimination.

Airway protection is paramount, and the threshold for tracheal intubation in the patient with seizures or other alterations in consciousness should be low. Assisted ventilation may be necessary if there is coingestion of a CNS depressant or if medications that depress respiratory drive, such as diazepam for seizures, are required for management.

If hypotension does not respond to an initial intravenous fluid bolus, propranolol may have a positive effect on blood pressure stabilization. If a vasopressor is also required, α-adrenergic agents such as phenylephrine or norepinephrine may be more efficacious; dopamine, which has some vasodilating properties at low doses, may be relatively ineffective.

Although no controlled clinical studies are available, there have been reports of success in treating tachydysrhythmias, particularly supraventricular tachycardias, with β-adrenergic antagonists, such as propranolol. Propranolol counters tachycardia, restores coronary blood flow, and interrupts the reentry phenomena that often underlie theophylline-induced dysrhythmias [33]. A potential hazard of propranolol administration is drug-induced bronchospasm; therefore, it should be used cautiously, if at all, in patients with significant reactive airways disease. Esmolol, an ultrashort-acting β_1-selective antagonist, has also been shown to be effective for select theophylline-induced tachydysrhythmias [63].

The antidysrhythmic agent adenosine has become the treatment of choice for supraventricular tachycardias and may be an important therapeutic addition in the management of theophylline-induced tachyarrhythmias. Having a significant effect on atrioventricular node conduction, adenosine can promptly reverse supraventricular tachycardias. Moreover, because of the evidence that adenosine and theophylline compete for the same receptor, adenosine may be a specific antidote for theophylline-induced supraventricular tachycardia. However, published clinical data in this regard are limited [64–66]. Amiodarone or lidocaine is the recommended treatment of ventricular irritability associated with hemodynamic compromise.

Seizures should be treated aggressively. High-dose benzodiazepine may be necessary for seizure termination. Phenytoin may be ineffective for theophylline-induced seizures [67], and in animal studies, it appears to contribute to theophylline-induced seizures. If seizures become prolonged, general anesthesia with a rapid-acting barbiturate, such as thiopental or pentobarbital, may be necessary. Neuromuscular blockade should be considered for seizures that are unresponsive to these modalities because significant morbidity may result from the rhabdomyolysis, hyperthermia, and acidosis of status epilepticus. There is some evidence that propranolol may help prevent or control theophylline-induced seizures [68].

Vomiting can be treated with the H_2-antagonist ranitidine, which reduces gastric acid hypersecretion [69,70]. Cimetidine administration is relatively contraindicated in theophylline poisoning because it inhibits theophylline metabolism. The dose of ranitidine is 50 to 100 mg given intravenously for adults and 0.1 to 0.5 mg per kg in children. Doses can be repeated every 6 to 8 hours. Metoclopramide also is an effective antiemetic that stimulates upper gastrointestinal motility and increases lower esophageal tone, without affecting theophylline clearance. The initial dose of metoclopramide is 0.5 to 1.0 mg per kg given intravenously for adults or 0.1 mg per kg for children (maximum, 1.0 mg per kg), although the risk of dystonia increases with increasing dose. Ondansetron is an alternative antiemetic, offering the advantage of effective antiemesis with no alterations in mental status and no risk of dystonic reaction. The phenothiazine antiemetics prochlorperazine and promethazine can lower seizure threshold and should not be administered.

Treatment of metabolic acidosis is aimed at maintaining a normal serum pH. For hypokalemia, it is important to emphasize that because hypokalemia's origin is predominantly the intracellular shift of potassium with minimal losses of total body potassium content through urine or vomitus, reversal of hypokalemia is best accomplished by lowering the theophylline concentration. Aggressive replacement of potassium may result in "overshoot" hyperkalemia [71]. Intravenous infusions of potassium chloride or potassium phosphate at 40 mEq per L in a saline solution should be adequate; intravenous boluses are usually not indicated. Hypophosphatemia, hypomagnesemia, hypercalcemia, and hyperglycemia rarely require correction.

Because vomiting is such a prominent feature of theophylline intoxication, there is rarely a need to perform gastric emptying. However, activated charcoal (see Chapter 117) is highly effective in reducing the absorption of theophylline and should be administered to all patients with recent ingestions. Whole-bowel irrigation (see Chapter 117) may be effective, particularly for sustained-release formulations, but its role in the treatment of theophylline intoxication remains undefined.

The repeated administration of activated charcoal (multiple-dose activated charcoal [MDAC]; see Chapter 117) is a valuable therapeutic measure for enhancing theophylline elimination [26,72–74]. Moreover, because MDAC acts through the principle of "gastrointestinal dialysis," it is effective even if theophylline intoxication occurs after intravenous administration of aminophylline [75]. MDAC is potentially as effective as hemodialysis in accelerating theophylline clearance [76,77]. However, it is not a substitute for hemodialysis in situations where rapid reduction in body theophylline burden is essential. All patients with significant theophylline intoxication should receive MDAC until the theophylline level is less than 15 µg per mL. Typical dosing is 1 g per kg charcoal every 4 hours (maximum, 50 g per dose). An effective alternative is 20 g every 2 hours [74]. Another alternative to bolus serial charcoal is administration via continuous nasogastric infusion at a rate of 0.25 to 0.50 g per kg per hour. Repeated vomiting, present in up to 80% of patients with theophylline intoxication [78], may delay or prevent successful MDAC administration. Aggressive antiemetic therapy is usually necessary.

In severely intoxicated patients or patients with moderate toxicity who are unable to tolerate MDAC, rapid removal of theophylline is essential. This is best accomplished by hemodialysis or hemoperfusion. If the need for extracorporeal drug removal is anticipated, a nephrologist should be involved early in management. Because of the time and personnel required to initiate extracorporeal drug removal, early notification can expedite the process once the decision has been made. Morbidity and mortality may be significantly lower if these procedures are undertaken before the onset of life-threatening disturbances. Indications for extracorporeal drug removal include hemodynamic instability or repeated seizures (regardless of serum theophylline concentration) and acute intoxication with a serum theophylline concentration greater than 80 µg per mL. Extracorporeal measures should be considered in patients younger than 6 months or older than 60 years with chronic intoxication and a theophylline concentration greater than 30 µg per mL.

Charcoal hemoperfusion has traditionally been considered the extracorporeal drug-removal method of choice for theophylline intoxication [79,80]. It reduces the elimination half-life of theophylline to as low as 0.7 to 2.1 hours [77], increasing clearance four- to sixfold [79]. However, hemoperfusion has significant risks, including hypotension, thrombocytopenia, red cell destruction, bleeding diathesis, and hypocalcemia. Also, there are few medical centers with the equipment and personnel needed to perform this procedure. The combination of scarce access to the procedure, increasing efficiency of hemodialysis, and the comparable efficacy of the two procedures has made hemodialysis the preferred procedure for treatment of severe theophylline intoxication [81].

Hemodialysis has many advantages over hemoperfusion. First, it is a technique that is widely available and relatively simple to perform. The need for administration of blood products is considerably less with hemodialysis. Dialysis can also increase theophylline clearance substantially, depending on the blood flow rates achieved by the device. Also, hemodialysis does not require the same degree of anticoagulation required by hemoperfusion, which lowers the risk of bleeding diathesis. Finally, the overall rate of complications is lower for hemodialysis than for hemoperfusion.

Peritoneal dialysis is an ineffective mode of drug removal in theophylline intoxication and is not recommended. Exchange transfusion, formerly thought to have no role in theophylline poisoning, has been used successfully in neonates with severe intoxication [82]. Other extracorporeal drug-removal methods, such as hemofiltration and plasmapheresis, have not been sufficiently evaluated, although there are case reports that these procedures have therapeutic value [83,84]. Hemofiltration, because it is a slow, passive, cardiac output-dependent technique, is unlikely to effect the rapid removal of theophylline that is necessary in severe intoxications.

CAFFEINE

Caffeine is a component of the three most popular beverages in the world: coffee, tea, and carbonated soft drinks. It is also used therapeutically as an antisleep aid and in many headache medications. Having a wide margin of safety and a relatively short elimination half-life—3 hours in adults, but 1 to 6 days in neonates—caffeine can be ingested daily in amounts as high as 1 g [85]. However, daily doses in this range are associated with unwanted adverse effects, including anxiety, jitteriness, and tachycardia.

The pharmacokinetic profile of caffeine resembles theophylline, with an important exception: whereas metabolism of theophylline (1,3-dimethylxanthine) produces inactive metabolites, caffeine (1,3,7-trimethylxanthine) undergoes 7-demethylation to form theophylline. Therefore, caffeine ingestion is invariably associated with measurable serum theophylline concentrations. After caffeine intoxication, serum theophylline concentration is a useful measure of toxicity. Many of the clinical manifestations of caffeine intoxication may in fact result from the effects of theophylline at its susceptible end organs.

The single ingestion of more than 1.5 g of caffeine (30 to 50 mg per kg in children) can produce serious adverse effects with the same manifestations found in acute theophylline intoxication [86]. Ingestions of more than 100 to 200 mg per kg are potentially lethal [85]. The five major disturbances occurring after caffeine intoxication are gastrointestinal, neurologic, metabolic, cardiac, and musculoskeletal [19]. Nausea and vomiting, with occasional hematemesis, predominate. CNS excitation may be manifested by anxiety, agitation, and seizures in severe cases. The same hypokalemia, hyperglycemia, and metabolic acidosis that appear after severe acute theophylline intoxication occur with caffeine poisoning. The most common cause of death after caffeine intoxication is intractable cardiac dysrhythmias [87]; severe acute overdoses have led to myocardial infarction [88]. Musculoskeletal effects can be prominent with caffeine intoxication; one feature is the appearance of severe rhabdomyolysis [89]. Life-threatening events after acute caffeine intoxication are associated with serum concentrations of more than 100 to 150 µg per mL. However, seizures after caffeine intoxication have occurred at serum concentrations as low as 50 µg per mL. Death has been reported with serum concentrations as low as 80 µg per mL. However, serum caffeine concentrations as high as 385 µg per mL have been associated with survival [90].

Management of caffeine intoxication follows the same principles as theophylline intoxication. Patient stabilization includes treatment of life-threatening seizures and cardiac dysrhythmias. Activated charcoal should be administered as soon as possible to provide gastrointestinal decontamination. Aggressive antiemetic therapy should be administered. MDAC is presumed to be equally effective for caffeine intoxication. Caffeine can be eliminated via hemodialysis; this procedure should be considered in those with seizures, cardiac dysrhythmias, or serum caffeine concentrations in excess of 100 µg per mL.

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CHAPTER 140 ■ OPIOID POISONING

ROBERT P. DOWSETT AND LUKE YIP□

Natural opioids (e.g., morphine and codeine) are harvested from the seedpods of the poppy plant *Papaver somniferum*. Semisynthetic opioids (e.g., dextromethorphan, heroin, hydrocodone, hydromorphone, oxycodone, and oxymorphone) are derivatives of morphine, whereas synthetic opioids (e.g., buprenorphine, butorphanol, diphenoxylate, fentanyl, meperidine, methadone, nalbuphine, pentazocine, propoxyphene, and tramadol) are not.

Clandestine laboratories have produced potent opioids as new manufacturing methods have been developed to circumvent the use of controlled or unavailable precursor compounds. Because these drugs may contain a wide variety of active ingredients, adulterants, and contaminants, the clinical syndromes seen in the abuser may be only partly related to the opioid component.

PHARMACOLOGY

Opioids interact with central nervous system (CNS) receptors to produce their analgesic, euphoric, and sedative effects. Historically, on the basis of animal studies, three major opioid receptors designated *mu*, *kappa*, and *sigma* have been proposed [1]. The *sigma* receptor is no longer considered an opioid subtype because it is insensitive to naloxone, has dextrorotatory stereochemistry binding, and has no endogenous ligand. The International Union on Receptor Nomenclature recommends a change from the Greek alphabet to one similar to other neurotransmitter systems; receptors are denoted by their endogenous ligand (*o*piates *p*eptides) with a subscript denoting their order of discovery: *delta* to OP_1 *kappa* to OP_2, and *mu* to OP_3 [2] (Table 140.1).

Most opioid analgesics are well absorbed after parenteral administration, from the pulmonary capillaries and mucosal sites. Analgesia is promptly achieved after parenteral administration and within 15 to 30 minutes after oral dosing. Peak plasma levels are generally attained within 1 to 2 hours after therapeutic oral doses. However, acute overdose may produce decreased intestinal peristalsis, resulting in delayed and prolonged absorption. Therapeutic and toxic serum drug concentrations are not well established.

All opioids undergo hepatic biotransformation, including hydroxylation, demethylation, and glucuronide conjugation. Considerable first-pass metabolism accounts for the wide variations in oral bioavailability noted with drugs such as morphine and pentazocine. Only small fractions of the parent drug are excreted unchanged in the urine. Active metabolites can contribute to the toxicological profile of specific drugs.

All opioids elicit the same overall physiologic effects as morphine, the prototype of this group. A typical morphine dose (5 to 10 mg) usually produces analgesia without altering mood or mental status in a patient. Sometimes dysphoria rather than euphoria is manifest, resulting in mild anxiety or a fear reaction. Nausea is frequently encountered, and vomiting is occasionally observed. Morphine and most of its congeners cause miosis in humans. This effect is exacerbated after an overdose, resulting in profound pupillary constriction, predominantly a central effect. Cerebral circulation does not appear to be altered by therapeutic doses of morphine unless respiratory depression and carbon dioxide retention result in cerebral vasodilation.

Respiratory failure is the most serious consequence of opiate overdose. Opioid agonists reduce the sensitivity of the medullary chemoreceptors in the respiratory centers to an increase in carbon dioxide tension and depress the ventilatory

□The views expressed do not necessarily represent those of the agency or the United States.

TABLE 140.1

OPIATE RECEPTOR SYSTEM AND CLINICAL EFFECTS

μ Opioid receptors (OP_3)	κ Opioid receptors (OP_2)	δ Opioid receptors (OP_1)
Supraspinal/spinal analgesia	Supraspinal/spinal analgesia	Supraspinal/spinal analgesia
Peripheral analgesia	Dysphoria	Modulation of OP_3 function
Sedation	Psychotomimesis	Respiratory depression
Euphoria	Diuresis	
Respiratory depression	Miosis	
Miosis		
Constipation		
Pruritus		
Bradycardia		
Prolactin release		
Growth hormone release		
Physical dependence		

response to hypoxia. Even small doses of morphine depress respiration, decreasing minute and alveolar ventilation [3]. The peak respiratory-depressant effect is usually noted within 7 minutes of intravenous (IV) morphine administration, but may be delayed up to 30 minutes if the drug is intramuscularly administered. Normal carbon dioxide sensitivity and minute volume usually return 5 to 6 hours after a therapeutic dose [3].

Therapeutic opiate doses cause arteriolar and venous dilation and may result in a mild decrease in blood pressure. This change in blood pressure is clinically insignificant while the patient is supine, but significant orthostatic changes are common [4]. Hypotension appears to be mediated by histamine release [5]. Myocardial damage (necrotizing angiitis) in opiate overdose associated with prolonged hypoxic coma may be mediated by cellular components released during rhabdomyolysis, direct toxic effects, or hypersensitivity to the opioids or adulterants [6].

Heroin (diacetylmorphine) has two to five times the analgesic potency of morphine [7]. Virtually all street heroin in the United States is produced in clandestine laboratories and adulterated before distribution (Table 140.2). The purity of street heroin is between 5% and 90%. Physiologically, the effects of heroin are identical to those described for morphine [8]. Heroin can be administered intravenously, intranasally, or inhaled as a volatile vapor, and can be mixed with other drugs of abuse, typically amphetamine or cocaine ("speed ball"). The plasma half-life of heroin is 5 to 15 minutes. Heroin is initially deacetylated in the liver and plasma, and then renally excreted as a conjugate, with small amounts of morphine, diacetylmorphine, and 6-monoacetylmorphine [8]. Individual variation in sensitivity and tolerance makes correlation of serum levels with clinical symptoms difficult.

The initial heroin rush is probably due to its high lipid solubility and rapid penetration into the CNS [8]. The majority of its lasting effects are attributable to its metabolites 6-monoacetylmorphine and morphine [8]. Fatal overdoses with heroin have been reported with serum morphine concentrations of 0.1 to 1.8 μg per mL [9].

Codeine (methylmorphine) is formulated as a sole ingredient and in combination with aspirin or acetaminophen. Codeine is rapidly absorbed by the oral route, producing a peak plasma level within 1 hour of a therapeutic dose [10]. Usually 10% of codeine is metabolized to morphine by CYP2D6; this may be greatly increased in patients with duplicated or amplified CYP2D6 genes, resulting in opioid toxicity [11]. This pathway may be inhibited by quinidine [12]. Clearance of codeine by CYP3A4 may be inhibited by clarithromycin and voriconazole [11]. Codeine and morphine appear in the urine within 24 to 72 hours. However, only morphine is detected in the urine at 96 hours [10]. The effect of codeine on the CNS is comparable with, but less pronounced than that of, morphine. Fatal ingestions with codeine alone are rare. The estimated lethal dose in a nontolerant adult is 800 mg, with a serum codeine concentration of 0.14 to 4.8 mg per dL [13].

Fentanyl, a phenylpiperidine derivative, has a potency 200 times that of morphine. Legitimate use is limited to anesthesia, and it is known to be commonly abused by hospital personnel. Rapid IV administration may result in acute muscular rigidity primarily involving the trunk and chest wall, which impairs respiration. Although motor activity resembling seizures has been associated with fentanyl use, simultaneous electroencephalogram recording during fentanyl induction of general anesthesia failed to show epileptiform activity [14]. This suggests a myoclonic rather than epileptic nature of the observed muscle activity [14].

Fentanyl is available as a transdermal delivery system that establishes a depot of drug in the upper skin layers, where it is available for systemic absorption. After removal of the patch, drug absorption from the dermal reservoir continues with an apparent half-life of 17 hours, versus 2 to 4 hours with IV administration [15].

By manipulating the chemical structure of fentanyl, α-methylfentanyl (China white), 3-methylfentanyl, and parafluoro-fentanyl have been produced and distributed on the street as heroin substitutes. They are 200 to 3,000 times more potent than heroin [16]. α-Methyl-acetyl-fentanyl, α-methylfentanyl acrylate, and benzylfentanyl are 6,000 times more potent than morphine [17].

TABLE 140.2

HEROIN ADULTERANTS

Mannitol	Antipyrine
Dextrose	Boric acid
Lactose	Mercurous salts
Talc	Animal manure
Sodium bicarbonate	Cocaine
Quinine	Amphetamine
Strychnine	Methamphetamine
Caffeine	Barbiturates
Phenacetin	Flour
Procaine	Magnesium sulfate
Lidocaine	Antihistamines
Benzocaine	Phencyclidine
Tetracaine	Scopolamine

Meperidine, another phenylpiperidine derivative, is less than half as effective when given orally as compared to the parenteral route [18]. It appears to be a common drug of abuse among medical personnel, yet there are few reports of meperidine poisoning or fatalities [19]. Peak plasma levels are 30 minutes after intramuscular administration, and 1 to 2 hours after an oral dose [18]. The duration of action is 2 to 4 hours [18]. Meperidine is metabolized primarily by *N*-demethylation to normeperidine, an active metabolite with half the analgesic and euphoric potency of its parent and twice the convulsant property [20]. Excretion is primarily through the kidneys as conjugated metabolites [21]. Meperidine and normeperidine may be detected in either urine or serum [21]. The seizures reported with meperidine toxicity have been attributed to the accumulation of normeperidine, which has an elimination half-life of 14 to 24 hours [18,22].

A synthetic meperidine analog, methyl-phenyl-propionoxypiperidine has been used as a heroin substitute. Methyl-phenyl-tetrahydropyridine, a contaminant produced during the clandestine synthesis of this agent, led to an epidemic of Parkinsonism among IV drug abusers within days of repeated injections [23].

Diphenoxylate is structurally similar to meperidine. Diphenoxylate (2.5 mg) is formulated with 0.025 mg atropine sulfate (Lomotil) and used in the treatment of diarrhea. In therapeutic doses, the drug has no significant CNS effects. Symptoms arising from a toxic ingestion may be delayed because of decreased gastrointestinal (GI) motility and accumulation of the hepatic metabolite difenoxin, a potent opioid with a long serum half-life [24]. The ingestion of only six to eight Lomotil tablets may cause serious toxicity in children [24].

Methadone is used for chronic pain conditions and maintenance of opiate addicts. It is well absorbed orally, producing a peak plasma level within 2 to 4 hours [25]. It has a prolonged but variable duration of action; the half-life averages 25 hours, but may be as long as 52 hours during long-term maintenance therapy [25]. As little as 40 to 50 mg may produce coma and respiratory depression in a nontolerant adult [26]. A protracted clinical course is expected after an overdose [27].

Propoxyphene is structurally related to methadone. It is available alone or in combination with aspirin or acetaminophen. Oral administration is followed by rapid absorption, with peak serum levels occurring in 1 hour [28]. The plasma half-life of propoxyphene and its main active metabolite, norpropoxyphene, is 6 to 12 hours and 37 hours, respectively. Norpropoxyphene is the primary metabolite excreted in the urine [29]. It is believed to play a role in the prolonged clinical course after an overdose [30]. Blood levels in fatal overdose cases range from 0.028 to 42.7 mg per L [31].

Pentazocine is a synthetic analgesic in the benzomorphan class and has been involved in the drug abuse trade [32]. It has agonist as well as weak antagonist activity at the opioid receptors. It has one third the analgesic potency of morphine [32]. Orally administered, pentazocine achieves peak plasma levels within 1 hour and is extensively metabolized in the liver with the parent compound and metabolites detectable in either urine or plasma [32]. Pentazocine (Talwin), in combination with the antihistamine tripelennamine, was known on the street as *T's and Blues* and was used as a heroin substitute [33].

In an attempt to curtail pentazocine abuse, the oral preparation was reformulated to contain 0.5 mg naloxone (Talwin-NX). When Talwin-NX is parenterally administered, the effects of pentazocine are antagonized by naloxone, which has precipitated withdrawal in opiate-dependent individuals. Because the duration of action of pentazocine exceeds that of naloxone, delayed respiratory depression may occur.

Dextromethorphan, an analogue of codeine, is found in a large number of nonprescription cough and cold remedies. It is available as a single ingredient but usually formulated in combination with sympathomimetic and antihistamine drugs. Dextromethorphan is well absorbed from the GI tract, with peak plasma levels occurring 2.5 and 6.0 hours after ingestion of regular and sustained-release preparations, respectively. The therapeutic effect is 3 to 6 hours, with a corresponding plasma half-life of 2 to 4 hours. The predominant antitussive effect is attributed to the active metabolite dextrorphan [34]. Within the therapeutic dose, dextromethorphan lacks analgesic, euphoric, and physical dependence properties [35].

Hydromorphone and oxycodone are orally administered opioids used in the treatment of chronic pain conditions. A number of sustained-release formulations are available, and can result in prolonged poisoning in overdose. A formulation of hydromorphone has recently been withdrawn from the market because alcohol could accelerate the release of the drug [36]. The sustained-release properties of some formulations of oxycodone can be circumvented by crushing or dissolving the tablet, resulting in fatal narcotic overdoses in drug abusers [37].

Tramadol is structurally similar to morphine. It is a centrally acting analgesic with moderate affinity for *mu* receptors. The metabolite *O*-demethyl-tramadol appears to have a higher affinity than the parent compound. Most of the analgesic effects are attributed to nonopioid properties of the drug, probably by blocking the reuptake of biogenic amines (e.g., norepinephrine and serotonin) at synapses in the descending neural pathways, which inhibits pain responses in the spinal cord [38].

Buprenorphine is a partial agonist activity with high affinity to, and slow dissociation from, the *mu* receptor. It displaces other opioids and its dose–response curve has a ceiling effect, resulting in less respiratory depression in overdose, although apnea may still occur [39,40]. It has poor oral bioavailability and is administered sublingually. It is also formulated with naloxone that is active only if administered intravenously [41]. Other partial agonists include butorphanol and nalbuphine. They can precipitate opioid withdrawal (see Chapter 145) in those taking other opioids.

CLINICAL PRESENTATION

Miosis, respiratory depression, and coma are the hallmarks of opiate intoxication, with the magnitude and duration of toxicity dependent on the dose and degree of tolerance. The clinical effects of an overdose with any one of the agents in this class are similar. However, there are important differences between certain drugs. Overdoses resulting in toxicity often have a prolonged clinical course, in part because of opiate-induced decreased GI motility when taken orally and prolonged half-life of the drug or its active metabolite(s). Miosis is considered a pathognomonic finding in opiate poisoning, with the exception of meperidine, propoxyphene, pentazocine, and dextromethorphan use, in the case of a mixed overdose with an anticholinergic or sympathomimetic drug, or when severe acidemia, hypoxemia, hypotension, or CNS structural disorder is present.

CNS depression occurs in most severely intoxicated patients. However, codeine, meperidine, and dextromethorphan intoxications are remarkable for CNS hyperirritability, resulting in a mixed syndrome of stupor and delirium. In addition, patients with meperidine toxicity may also have tachypnea, dysphoric and hallucinogenic episodes, tremors, muscular twitching, and spasticity, whereas patients with dextromethorphan toxicity may also manifest restlessness, nystagmus, and clonus [22,42].

Pulmonary edema may complicate the clinical course of opioid overdose and appears more prevalent with heroin, morphine, codeine, methadone, and propoxyphene [13,43,44]. Pulmonary edema has occurred in postoperative patients who received naloxone and after naloxone therapy in overdose patients [45,46]. However, naloxone does not appear to alter the

TABLE 140.3

PULMONARY COMPLICATIONS ASSOCIATED WITH OPIATE ABUSE

Pulmonary arteritis (cotton)	Bacterial pneumonia
Pulmonary thrombosis (talc)	Aspiration pneumonitis
Pulmonary hypertension (talc)	Pulmonary edema
Septic emboli	Atelectasis
Lung abscess	Respiratory arrest

vascular permeability of the lung directly [47]. Typically, the patient has a depressed consciousness and respiration. After naloxone administration, the patient awakens and over minutes to hours is noted to become hypoxic and develop pulmonary edema. Acute naloxone-induced withdrawal has been associated with massive CNS sympathetic discharge, which may be a precipitating factor in the development of neurogenic pulmonary edema [48]. It appears that the pulmonary injury is at the alveolar–capillary membrane, resulting in manifestations consistent with acute respiratory distress syndrome [49]. It does not appear to be an immune-mediated mechanism [50]. Pulmonary edema may present within 2 hours of parenteral heroin use, up to 4 hours after intranasal heroin use, and up to 24 hours after methadone overdose [51].

Patients with heroin-induced pulmonary edema typically have normal capillary wedge pressures and elevated pulmonary arterial pressures [52]. In contrast, elevated systemic, pulmonary arterial, and pulmonary capillary wedge pressures and total systemic vascular resistance are seen with pentazocine intoxication [53]. This effect is believed to result from transient endogenous catecholamine release [54]. Persistent pulmonary symptoms beyond 24 to 48 hours may indicate aspiration or bacterial pneumonitis, with atelectasis, fibrosis, bronchiectasis, granulomatous disease, or pneumomediastinum [55]. Adulterants in street drugs are potential pulmonary toxins [56]. Dyspnea, hypoxemia, and the presence of multiple reticulonodular infiltrates on chest radiograph may be caused by adulterants in the IV mixture. A summary of the potential pulmonary complications associated with opioid abuse is provided in Table 140.3.

Heroin toxicity may be associated with cardiac conduction abnormalities and dysrhythmias, which may be the result of metabolic derangements associated with hypoxia, a direct effect of the abused agent, or adulterants (e.g., quinine) in street drugs [57–59].

Leukoencephalopathy associated with inhalational abuse of heroin ("chasing the dragon") typically progresses for several weeks. Initially, cerebellar ataxia and motor restlessness may be followed by the development of pyramidal tract lesions, pseudobulbar reflexes, spastic paresis, myoclonic jerks, and choreoathetoid movements. A quarter of patients may progress to hypotonic paresis, akinetic mutism, and death [60].

Seizures and focal neurologic signs are usually absent after opiate intoxication [61] unless precipitated by severe hypoxia, an intracranial process (e.g., brain abscess and subarachnoid hemorrhage), proconvulsive adulterants, meperidine, propoxyphene, pentazocine (T's and Blues), or tramadol use [33,62–65]. Meperidine- and propoxyphene-related seizures may become more frequent in chronic drug abusers with renal insufficiency.

Disabling myoclonus has been reported after several days of fentanyl therapy by the transdermal delivery system [17].

The clinical course after propoxyphene overdose may be severe and rapidly progressive, with cardiac dysrhythmias, circulatory collapse, seizures, and respiratory arrest developing within 45 minutes [66]. Seizure may be focal or generalized [62]. Propoxyphene appears to be responsible for CNS toxicity (respiratory depression and seizures) and cardiac toxicity (QRS prolongation and dysrhythmias) [67], whereas norpropoxyphene contributed only to the cardiotoxicity in one animal study [68]. Cardiotoxicity may be exacerbated by hypoxia or adulterants (e.g., quinine) in street drugs. The minimum toxic dose reported is 10 mg per kg, and 20 mg per kg is considered potentially fatal, but tolerance develops with chronic use [69]. Doses of 1,000 to 2,000 mg can be ingested or injected, with minimal signs of intoxication in chronic propoxyphene abusers and heroin addicts [70].

Anxiety, dysphoria, and hallucinations are more common with pentazocine than with other opiate derivatives [32]. Acute toxicity in combination with tripelennamine results in the typical opiate intoxication syndrome as well as dyspnea, hyperirritability, hypertension, and seizures. It is believed that these effects may be directly related to tripelennamine [33].

Hypotension may occur after opiate overdose, although pentazocine intoxication may result in hypertension [33]. Heroin and propoxyphene toxicity may be associated with nonspecific ST-segment and T-wave changes, first-degree atrioventricular block, atrial fibrillation, prolonged QTc intervals, and ventricular dysrhythmias [57]. Cardiovascular findings may be exacerbated by hypoxia or adulterants (e.g., quinine) in street drugs.

Dextromethorphan abuse seems to be self-limiting because of adverse drug events, such as lethargy, somnambulism, and ataxia [71]. It is associated with a psychologic rather than physiologic dependence syndrome [72]. Recreation dextromethorphan abusers report increased perceptual awareness, altered time perception, euphoria, and visual hallucinations [71]. Long-term use may result in bromide toxicity [73]. Because dextromethorphan frequently appears in combination products, the contribution of these coingestants should be considered.

Methadone can produce bradycardia, QTc prolongation, and torsades de pointes. Bradycardia has been reported infrequently and is postulated to be because of methadone's structural similarity to verapamil [74,75]. QTc prolongation and torsades de pointes have been associated with mean daily methadone dose 397 ± 238 mg; mean QTc interval on presentation was 615 ± 77 ms. In one case series, the majority of patients were receiving a potentially QT-prolonging drug, 41% of the patients had hypokalemia, and 18% of the patients were found to have structural heart disease [76]. A proposed mechanism is inhibition of the cardiac potassium channel by the nontherapeutic (S)-methadone isomer [77]. This isomer is metabolized by CYP2B6; 6% of the population are slow metabolizers, resulting in elevated levels of (S)-methadone and increased QTc intervals [77,78].

The onset of anticholinergic and opioid effects may be significantly delayed after a diphenoxylate overdose [79]. Atropine effects (CNS excitement, hypertension, fever, and flushed dry skin) occur before, during, or after opioid effects. However, opioid effects (CNS and respiratory depression with miosis) may predominate or occur without any signs of atropinism. Cardiopulmonary arrest has been reported to occur 12 hours after ingestion of diphenoxylate [80].

Patients presenting after a tramadol overdose may exhibit lethargy, nausea, tachycardia, agitation, seizures, coma, hypertension, respiratory depression metabolic acidosis, acute hepatic failure, and acute renal failure [81]. Tramadol-associated seizures are brief, and significant respiratory depression is uncommon [65].

Interaction between meperidine and monoamine oxidase inhibitors (MAOIs), dextromethorphan and MAOIs, and tramadol and selective serotonin reuptake inhibitors may result in the serotonin syndrome [82–84]. Patients with severe serotonin syndrome exhibit rapid onset of altered mental status, muscle

rigidity, hyperthermia, autonomic dysfunction, coma, seizures, and death.

Rhabdomyolysis, hyperkalemia, myoglobinuria, and acute renal failure may complicate the clinical course of an acute opioid overdose [85]. Acute renal failure may be due to direct insult by the abused substance, adulterants in street drugs, and prolonged coma [58,85]. Chronic parenteral drug use may result in glomerulonephritis and renal amyloidosis and has been associated with concurrent bacterial infections [86]. Potential lethal acute infections have been linked to clostridia contamination [87].

Body packers or "mules" are people who transport large numbers of concentrated heroin packets in their GI tract from one country to another. If one of these packets ruptures, the amount of drug released can cause severe and prolonged toxicity [88]. They may also develop features of intestinal obstruction and, occasionally, intestinal perforation and peritonitis [89].

DIAGNOSTIC EVALUATION

Laboratory studies such as complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine and creatine phosphokinase, urinalysis, arterial blood gas, electrocardiography, chest and abdominal radiography, head computed tomography, and lumbar puncture should be obtained as clinically indicated. Arterial blood gas usually reflects hypoventilation, respiratory acidosis, and metabolic acidosis [90]. If pulmonary edema develops, chest radiographs typically reveal bilateral fluffy alveolar infiltrates, occasionally unilateral in nature, and echocardiograms show normal cardiac function [43]. A markedly negative anion gap with hyperchloremia should raise the suspicion of bromide poisoning from chronic dextromethorphan use [73]. Chest radiographic findings of pulmonary edema usually resolve within 24 to 48 hours.

It is recommended that an ECG be obtained prior to commencing methadone therapy and within 30 days of commencement and then yearly to monitor the QTc interval [91].

Leukoencephalopathy associated with inhalational abuse of heroin appears as hypoattenuation in the affected white matter, although this may not be apparent until late in the disease. Magnetic resonance imaging typically demonstrates white matter hyperintensity on T2-weighted sequences. Affected areas are initially the occipital and cerebellar white matter, followed by involvement of the parietal, temporal, and frontal lobes. The cerebellar peduncles, splenium of the corpus callosum, posterior limb of the internal capsules, corticospinal tract, medial lemniscus, and tractus solitarius may also be involved [60].

TABLE 140.4

INFECTIOUS COMPLICATIONS IN INTRAVENOUS DRUG ABUSERS

Endocarditis	Lymphadenitis
Aspergillosis	Epidural abscess
Bacterial meningitis	Phlebitis
Cutaneous abscess	Viral hepatitis
Mycotic aneurysm	Wound botulism
Cellulitis	Tetanus
Brain abscess	Osteomyelitis
Lymphangitis	Septicemia
Subdural abscess	HIV/AIDS

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Quantitative serum opiate levels do not contribute to patient management. A urine toxicology screen may confirm the diagnosis, but is rarely necessary for acute patient management. Commercial opioid assays are unlikely to detect synthetic opioids. The metabolites of naloxone are chemically related to oxymorphone, but naloxone is not known to give false-positive immunoassay urine screens for opioid substances [92]. False-positive serology tests for syphilis have been reported among drug addicts [93]. Laboratory investigation should also include tests for infection in patients with fever (Table 140.4).

MANAGEMENT

A diagnosis of opioid poisoning should be considered in all comatose patients. However, the classic triad of opiate toxicity (coma, miosis, and respiratory depression) may not be apparent after a mixed overdose. Respiratory support is paramount in the management of patients with opioid toxicity; one should secure the airway and ventilate with 100% oxygen. Vascular access should be established. The patient should be placed on continuous pulse oximetry and cardiac monitoring. Vital signs should be monitored frequently.

Naloxone is a specific opiate receptor antagonist and can reverse the analgesia, respiratory depression, miosis, hyporeflexia, and cardiovascular effects of opiate toxicity [94,95]. The goal of naloxone therapy is to reestablish adequate spontaneous ventilation. The initial IV naloxone dose should be 0.1 mg if the patient is possibly opioid dependent; larger doses may precipitate acute opioid-withdrawal syndrome. Otherwise, an initial 2 mg dose can be administered. If there is history of an opiate exposure, a strong suspicion based on presenting signs and symptoms, or a partial response to the initial naloxone dose, repeated IV naloxone boluses up to 10 mg should be administered because methadone, pentazocine, propoxyphene, diphenoxylate, and sustained-release preparations of oxycodone and hydromorphone may not respond to the usual naloxone doses [96,97]. Despite its strong affinity to *mu* receptors, buprenorphine overdose can be treated effectively with normal doses of naloxone [40].

Intramuscular, intralingual, endotracheal, intraosseous, and intranasal routes of naloxone administration are acceptable alternatives when IV access is not readily available [96,98–100]. Repeat naloxone boluses may be required every 20 to 60 minutes because of its short elimination half-life (60 to 90 minutes). A continuous naloxone infusion should be considered in patients who have a positive response but require repeated bolus doses because of recurrent respiratory depression [100,101]. A therapeutic continuous naloxone infusion can be made by administering two third of the effective naloxone bolus dose per hour. The infusion is titrated to maintain adequate spontaneous ventilation without precipitating acute opioid withdrawal and empirically continued for 12 to 24 hours. The patient should be admitted to an intensive care or high-dependency setting for continuous monitoring. After the naloxone therapy is discontinued, the patient should be carefully observed for 4 hours for recurrent respiratory depression.

Naloxone is effective in reversing diphenoxylate-induced opioid toxicity. However, recurrence of respiratory and CNS depression is common [79]. All patients with significant diphenoxylate overdose should be observed in an intensive care setting for at least 24 hours.

Hypotension may respond to naloxone therapy but may require fluid resuscitation and vasopressors. Overzealous fluid resuscitation should be avoided because of the risk of pulmonary edema.

The management of seizures should follow present treatment guidelines and include benzodiazepines or barbiturates.

Adjunct naloxone therapy may be effective in propoxyphene, but not in meperidine- or tramadol-related seizures [102]. Seizures have been reported after naloxone administration for tramadol overdose [65].

The management of serotonin syndrome is primarily supportive (see Chapters 66 and 124). Sedation, paralysis, intubation and ventilation, anticonvulsants, antihypertensives, and aggressive rapid cooling may all be necessary. Some success has been obtained with the nonspecific serotonin antagonist cyproheptadine (4 to 8 mg every 8 hours orally) or olanzapine (sublingual 10 mg) [103,104].

GI decontamination should be considered for orally administered opioids after vital signs have been stabilized. The clinical benefits of multiple oral doses of activated charcoal are unproven, but it is potentially beneficial because of the prolonged absorption phase that is typically encountered with opiate overdoses. Repeat charcoal doses should not be used in the absence of active bowel sounds.

The management of pulmonary edema should include adequate ventilation, oxygenation, and positive-pressure ventilation as needed [105]. Inotropic agents and diuretics are of little value.

Bradycardia secondary to methadone administration responds to ceasing the drug; atropine has not been utilized [75]. If patients receiving methadone develop a QTc interval of more than 500 milliseconds, consideration should be given to reducing the dose or discontinuing the drug [91].

Asymptomatic body packers should be conservatively managed when the condition of packaging does not appear to be compromised. One proposed guideline involves the oral administration of a water-soluble contrast solution followed by serial abdominal radiographs (Table 140.5) [106]. Whole-bowel irrigation (WBI) with polyethylene glycol electrolyte lavage solution (PEG-ELS) has also been advocated on the basis of case reports [107].

Pruritus is a common opioid adverse drug event. It may be localized or general, and ranges from mild to severe. Antihistamines are usually ineffective, but naloxone has frequently been found to offer relief. Ondansetron has been reported to provide relief in refractory cases [108].

TABLE 140.5

MEDICAL MANAGEMENT FOR ASYMPTOMATIC BODY PACKERS

1. Administer an oral dose of water-soluble contrast (e.g., Gastrografin): 1 mL/kg[a]
2. Perform abdominal radiographs (supine and upright) at least 5 h after oral contrast administration
3. If radiographs are positive, perform daily abdominal radiographs, and after a spontaneous bowel movement
4. All bowel movements are checked for drug packets
5. The patient may be discharged after passage of two packet-free bowel movements *and* negative abdominal radiographs

[a]Patients are permitted to feed normally, and vascular access should be maintained.

Leukoencephalopathy associated with inhalational abuse of heroin has been reported to improve following the antioxidant ubiquinone (coenzyme Q10) administration in doses of 30 to 300 mg QID [109].

Nalmefene is also effective for the reversal of opioid-induced CNS effects and can be administered orally or intravenously. Its half-life and dose-dependent duration of action are 4 to 8 hours after IV administration [110]. The initial adult dose is 0.5 mg for those who are not opioid dependent and 0.1 mg for those suspected of having opioid dependency. If there is an incomplete response or no response, additional doses can be given at 2- to 5-minute intervals. A total dose of 1.5 mg may be necessary to exclude the possibility of opioid poisoning. The principal advantage over naloxone is its considerably longer duration of antagonistic action however; withdrawal syndromes precipitated by nalmefene use would also be prolonged.

Naltrexone is a potent, long-acting pure opiate antagonist that is effective orally. Its use is primarily limited as adjunctive therapy for opioid detoxification. Naltrexone may induce a withdrawal syndrome that lasts up to 72 hours.

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CHAPTER 141 ■ PESTICIDE POISONING

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A pesticide is as an agent intended for killing, preventing, repelling, or mitigating any pest. With the increasing use, environmental contamination and reports of epidemic pesticide poisoning are inevitable [1–3]. The health consequences from the long-term and low-level exposure to these chemicals, such as carcinogenesis [4,5], teratogenicity [6], fertility [7], and neurologic sequelae [8,9], may be significant and immeasurable. In many countries in which there are limited regulations on pesticide usage, pesticide ingestion is one of the leading forms of suicide, and pesticide exposure is a major occupational risk [10–12]. Even in the United States, pesticide exposures remain a major public health problem [13]. The World Health Organization estimated that accidental and occupational pesticide poisonings worldwide account for 1.5 million cases and 28,000 deaths annually [14].

This chapter focuses on selected pesticides that are most clinically important. Some of the common pesticides are provided in Table 141.1. Organophosphate insecticides are covered in Chapter 128. Further information on the identification and toxicity of pesticide products may be obtained from sources such as material data safety sheets, *Hayes' Handbook of Pesticide Toxicology, Farm Chemicals Handbook*, and the pesticide label database (http://www.cdpr.ca.gov/docs/label/labelque.htm).

ORGANOCHLORINES

Organochlorines are commonly used as insecticides, soil fumigants, solvents, and herbicides. Human toxicity can result from either acute or chronic exposure. Contamination typically occurs during production and application of these agents. Infants and toddlers are at risk for toxicity from bioaccumulation in foodstuffs, excretion in breast milk, and concentration in fetal tissues [15–17]. These toxicants can cause a variety of systemic manifestations, but are most notable for their central nervous system (CNS) effects. Organochlorines can be divided into four structural categories: dichlorodiphenyltrichloroethane (DDT) and related agents, hexachlorocyclohexanes, cyclodienes, and toxaphenes.

DDT is a well-known organochlorine. It was a popular insecticide in the agricultural industry during the 1960s. The many environmental concerns related to the use of DDT, including carcinogenesis, bioaccumulation, and other health risks to humans and animals, led to the banning of its use in the United States as of 1972. DDT is no longer being produced in the United States. Dicofol (a miticide) and methoxychlor are structurally related to DDT. The cyclodienes include chlordane, heptachlor, endrin, aldrin, and dieldrin. The use of several of these insecticides in the United States was discontinued between 1988 and 1990. Some of the other organochlorines that are structurally related to the cyclodienes include endosulfan, chlordecone, kelevan, and mirex. Endosulfan is considered highly toxic and is registered for agricultural, but not residential, use in the United States [18]. Mirex and chlordecone (Kepone) are no longer being used in the United States.

Pharmacology

The organochlorines are well absorbed from the gastrointestinal (GI) tract. For example, death can occur within 2 hours of intentionally ingesting endosulfan, and most deaths associated with chlordane have been from oral exposures in children. The serum half-lives of these chemicals are long, varying from days to months, because of their high lipid solubility. This allows these agents to be stored in fatty tissues (e.g., brain), with the resultant delay in total body clearance. The organochlorines are known to concentrate in breast milk and fetal tissue. At delivery, it has been shown that fetal blood and tissue had higher concentrations of lindane (γ-hexachlorocyclohexane, Kwell) than maternal samples [16,17]. However, teratogenic effects have not been demonstrated in the limited number of animal studies performed [19].

Organochlorines are metabolized by the microsomal enzymes in the liver. Toxaphene, chlordane, DDT, and lindane can induce microsomal enzyme activity and affect not only their own metabolism but also the effects of coadministered medications [20].

Chlordane has several metabolites, such as heptachlor, oxychlordane, and heptachlor epoxide. Most of the available information on chlordane and metabolite tissue distribution is from case reports of accidental and suicidal exposures. Depending on the source, the elimination half-life of chlordane varies from 21 to 88 days [21,22]. Most of the chlordane and metabolites are excreted by the biliary system. On absorption into the body, aldrin is rapidly metabolized to the epoxide derivative, dieldrin. Because very little of aldrin remains, its toxicity is attributed to dieldrin. Dieldrin is stored in fatty tissues, and its elimination half-life in humans is approximately 369 days [23]. Endrin, an isomer of dieldrin, is rapidly metabolized in both humans and animals, with an elimination half-life of 2 to 6 days [24].

TABLE 141.1

COMMON PESTICIDES

- Inorganic and organometal pesticides
  - Aluminum phosphide
  - Antimony potassium tartrate
  - Arsenical pesticides
  - Barium carbonate
  - Boric acid
  - Calcium chloride
  - Copper sulfate
  - Elemental mercury
  - Elemental sulfur
  - Lead arsenate
  - Mercuric chloride
  - Methylmercury
  - Phosphorus
  - Sodium chlorate
  - Sodium dichromate
  - Thallium sulfate
  - Zinc chloride
  - Zinc phosphide
- Pyrethrins, pyrethroids, and plant-derived pesticides
  - Anabasine
  - Barthrin
  - Blasticidin S
  - Cartap
  - Chlordecone
  - Cyfluthrin
  - Cyfluthrinate
  - Cyhalothrin
  - Cypermethrin
  - Decamethrin
  - Deltamethrin
  - Fluvalerate
  - Fluvalinate
  - Nicotine
  - Phenothrin
  - Pyrethrins
  - Resmethrin
  - Ricin
  - Rotenone
  - Sabadilla
  - Strychnine
  - Tralocythrin
  - Tralomethrin
- Fumigants and nematocides
  - Acrylonitrile
  - Aluminum phosphide
  - Boron trifluoride
  - Carbon disulfide
  - Carbon tetrachloride
  - Chloropicrin
  - 1,2-Dibromoethane
  - 1,2-Dichloroethane
  - *p*-Dichlorobenzene
  - 1,2-Dichloropropane
  - 1,3-Dichloropropene
  - Epoxyethane
  - Hydrogen cyanide
  - Methylbromide
  - Naphthalene
  - 1,1,1-Trichloroethane
  - Trichloroethylene
- Synthetic organic rodenticides
  - ANTU
  - Brodifacoum
  - Chloralose
  - Difenacoum
  - Diphacinone
  - Fluoroacetamide
  - Fluoroethanol
  - Norbormide
  - Pyriminil
  - Sodium fluoroacetate
  - Warfarin
- Herbicides
  - Amitrole
  - Atrazine
  - Bromoxynil
  - Cycloate
  - Dicamba
  - Dichlobenil
  - 2,4-Dichlorophenoxyacetic acid
  - Diquat
  - Diuron
  - Ioxynil
  - MCPA
  - Mecoprop
  - Molinate
  - Phenmedipham
  - Paraquat
  - Propanil
  - Propazine
  - Pyrazon
  - Silvex
  - Simazine
  - TCA
  - 2,3,5-Trichlorophenoxyacetic acid
- Fungicides and biocides
  - Benomyl
  - Captafol
  - Captan
  - 1-Chloro dinitrobenzene
  - Dichloran
  - Diphenyl
  - Maneb
  - Organotins (tributyltin)
  - Quintozene
  - Tetrachlorophthalide
  - Thiabendazole
  - Thiram
  - Thiophanate-methyl
  - Zineb
  - Ziram
- Organochlorine insecticides
  - Aldrin
  - Chlordane
  - Chlorobenzilate
  - Chlordecone
  - DDT
  - Dicofol
  - Dieldrin
  - Endrin
  - Endosulfan
  - Ethylan
  - Heptachlor
  - Hexachlorobenzene
  - Isobenzan
  - Kelevan
  - Kelthane
  - Lindane (γ -hexachlorocyclohexane)
  - Mirex
  - Methoxychlor
  - TDE
  - Toxaphene
- Organophosphate insecticides
  - Azinphos-methyl
  - Carbophenothion
  - Carejin
  - Chlorfenvinphos
  - Chlorphoxim
  - Chlorpyrifos
  - Demeton
  - Demeton-methyl
  - Dialifos
  - Diazinon
  - Dicapthon
  - Dichlofenthion
  - Dichlorvos
  - Dicrotophos
  - Dimefox
  - Dioxathion
  - Edifenphos
  - Endothion
  - Fenitrothion
  - Fensulfothion
  - Fenthion
  - Fonofos
  - Formothion
  - Jodfenphos
  - Leptophos
  - Malathion
  - Merphos
  - Methidathion
  - Mevinphos
  - Mipafox
  - Monocrotophos
  - Naled
  - Oxydemeton-methyl
  - Parathion
  - Parathion-methyl
  - Phenthoate
  - Phorate
  - Phosalone
  - Phosphamidon
  - Phoxim
  - Pirimiphos-methyl
  - Schradan
  - Temephos
  - Thiometon
  - Trichlorfon
- Carbamates
  - Aldicarb
  - Bendiocarb
  - 4-Benxiothielyn-*N*-methylcarbamate
  - Bufencarb
  - Carbaryl
  - Carbofuran
  - Dioxacarb
  - Isolan
  - 3-Isopropyl phenyl-*N*-methylcarbamate
  - Landrin
  - Methomyl
  - Mexacarbate
  - Oxamyl
  - Phencyclocarb
  - Promecarb
  - Propoxur
- Miscellaneous pesticides
  - Azoxybenzene
  - Busulfan
  - Chlorambucil
  - Chlordimeform
  - Chlorfenxon
  - DEET
  - 5-Fluorouracil
  - Hexamethylmelamine
  - Metaldehyde
  - Methotrexate
  - Porfiromycin
  - Propargite
  - Thiotepa
- Nitro compounds and related phenolic pesticides
  - Binapacryl
  - Dinocap
  - 2,4-Dinitrophenol
  - Dinoseb
  - Pentachlorophenol
  - TCDD

ANTU, α-naphthylthiourea; DDT, dichlorodiphenyltrichloroethane; DEET, *N*-*N*-diethyl-*m*-toluamide; MCPA, 4-chloro-2-methylphenoxyacetic acid; TCA, trichloroacetic acid; TCDD, tetrachlorodibenzodioxin; TDE, 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane.
Classifications adapted from Hayes WJ Jr, Laws ER (eds): *Handbook of Pesticide Toxicology.* San Diego, Academic, 1991.

TABLE 141.2

ORGANOCHLORINE LEVELS OF TOXICITY

High	Endrin, dieldrin, aldrin, endosulfan
Moderate	Chlordecone, heptachlor, chlordane, toxaphene, dichlorodiphenyltrichloroethane, hexachlorobenzene
Low	Methoxychlor, perthane, kelthane, chlorobenzilate, mirex

Organochlorines have several mechanisms of action. They alter sodium- and potassium channel movement across the neuronal membranes and can be considered axonal toxins. With DDT, sodium ion transport is facilitated and potassium transport is inhibited. This results in the spontaneous firing and prolongation of action potentials and repetitive firing after a stimulus. DDT also inhibits Na^+/K^+ adenosine triphosphatase and calmodulin activities, which reduces the rate of neuronal repolarization. This may account for some of the neurologic manifestations such as paresthesias, thought disturbances, myoclonus, and seizures. Cyclodienes, hexachlorocyclohexanes, and toxaphenes manifest neurotoxicity by inhibiting γ-aminobutyric acid receptor function in the CNS [25]. In the limbic system, lindane can directly excite neurons and result in agitation and seizures [25,26]. Abnormalities in respiratory rate patterns can result from direct medullary toxicity or pulmonary aspiration. The level of toxicity of the various organochlorines can be categorized into high, moderate, and low (Table 141.2).

Clinical Toxicity

Poisoning can result from ingestion, dermal absorption, or inhalation. Inadvertent human exposures to aldrin and dieldrin have resulted from pesticide spraying, which causes dermal and inhalational absorption. The use of lindane in home vaporizers has resulted in significant inhalation toxicity [27]. Agents such as dieldrin, lindane, and Kepone have good dermal penetration. Workers who directly handled lindane had health complaints of headaches, paresthesias, tremors, confusion, and memory impairment [28]. Also, seizures have been reported in occupational surveys among sprayers and applicators of aldrin and dieldrin [29,30]. As little as two total body applications on two successive days of 1% lindane (Kwell), a common scabicide, resulted in seizures in an 18-month-old child [31]. The peak concentration of lindane occurs 6 hours after dermal application; thus, delayed and prolonged manifestations of toxicity may occur from dermal absorption. Dermatitis can occur from the topical exposure to dicofol and methoxychlor [24]. Intradermal and subcutaneous injections of these agents can result in chemical dermatitis and sterile abscesses [32]. Dicofol and methoxychlor have minimal toxicity. Human volunteers ingesting up to 2 mg per kg per day of methoxychlor for 8 weeks did not demonstrate any ill effects [33].

Seizures are the most prominent CNS effect of these agents. The seizures occur soon after exposure, may present without a prodrome, and can be quite protracted in frequency [24,34–38]. Late-onset seizures may result from delayed GI or dermal absorption. Acute exposures to DDT present initially with tremors, nausea, vomiting, muscle weakness, and confusion, which may progress to seizures [39]. Among the organochlorines, both psychomotor agitation and CNS depression have been described. Chlordecone, mirex, and endosulfan are more likely to cause tremors and agitation than seizures. Kelthane, perthane, methoxychlor, and lindane are more likely to cause CNS sedation than excitation. Endrin is considered one of the most toxic of the chlordienes, with reports of hyperthermia and decerebrate posturing [24]. In 1984, an outbreak of endrin toxicity from contaminated foodstuffs occurred in Pakistan, where seizures resulted in a 10% mortality rate [36].

Neurologic symptoms resolve quickly because of rapid distribution of the organochlorines from blood to lipid stores. Because redistribution back into the blood pool can occur at a later time, continual observation of the patient for delayed toxicity may be warranted. Some of the long-term CNS effects (i.e., thought disturbances) after significant exposures may be due to direct chemical toxicity or anoxic encephalopathy from sustained seizures [40]. Chlordecone is a recognized neurotoxin, causing peripheral neuropathies [41].

Nausea, vomiting, and diarrhea may occur after ingestions, especially if petroleum distillates are part of the preparation. Pulmonary aspiration of these agents can cause tachypnea and significant respiratory distress, with resultant pulmonary edema [40]. When dicofol is heated or comes in contact with an acid, it decomposes to hydrogen chloride, which causes respiratory irritation [24]. Hypersensitivity pneumonitis may result from inhalational exposures when the organochlorine is mixed with pyrethrins.

Cardiac dysrhythmias, including ventricular fibrillation, have been reported from organochlorine exposure [42]. Halogenated hydrocarbons sensitize the myocardium to catecholamines, which results in a variety of rhythm disturbances. Cardiotoxicity can be exacerbated by either stress-provoking events or the exogenous administration of catecholamines. In severely ill patients, other causes of cardiac dysrhythmias, such as hypoxia and acidemia, should be considered.

Significant elevations in liver enzymes were reported in a group of 19 workers with a 10-year lindane exposure [43]. Animal studies with acute oral exposures to lindane have demonstrated fatty degeneration and necrosis of the liver [44]. From the few reports of human exposures to chlordane, there is little evidence of hepatotoxicity from this agent [21,45,46]. Microsomal enzyme induction has been demonstrated in animals that were orally administered chlordane. Long-term exposure among 233 workers with aldrin, dieldrin, endrin, and telodrin for 4 to 12 years was not associated with any significant elevation of hepatic enzymes or hepatic enzyme induction.

Hematologic dyscrasias, including aplastic anemia, leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, thrombocytopenia, and pancytopenia, have been reported after repeated lindane exposures [27,47]. However, all of the involved preparations also contained benzene, which can account for such findings. Megaloblastic anemia and bone marrow depression have been associated with chlordane exposures. DDT and toxaphene are suspected human carcinogens [48,49]. The risks for aldrin and dieldrin as human carcinogens could not be determined by the International Agency for Research on Cancer because of insufficient human and animal data [48].

Diagnostic Evaluation

Serum and urine concentrations of these organochlorines are commonly measured by gas chromatography or mass spectrometry. In an obvious exposure, these measurements are academic and would not alter clinical management. There are no correlations between concentrations in body tissues and specific health effects. If the diagnosis is in doubt, these measurements can at least confirm or rule out the insecticide exposure. Although blood is commonly sampled for the detection of these chemicals, adipose tissue or human milk may be used as well [50]. The laboratory should be consulted regarding the availability of analytical methods for biological specimens other

than blood. An acute exposure can be determined by a quantitative comparison of parent compound to metabolite. Because DDT and aldrin are rapidly metabolized on systemic absorption, their elevated concentrations in the blood would support a recent exposure.

Chlorinated hydrocarbons are radiopaque, and their radiopacity is directly related to the number of chlorine atoms per molecule. Thus, radiographs can assist in demonstrating aspiration pneumonia and gut burden.

Management

Rescue workers and health care providers must use proper equipment, such as gloves and gowns, to prevent unnecessary exposure to these chemicals when providing assistance to these patients [51]. Initial treatment of organochlorine exposure involves limiting further chemical absorption by the patient. The patient should be removed from the scene, disrobed, and thoroughly and repeatedly washed with soap and water. Washing should include hair and fingernails. The patient's clothing and leather goods must be placed in a plastic bag and discarded because of the tenacious binding of these agents to leather. All wash water should be contained and discarded in a secure fashion.

The role of gastric decontamination depends on the clinical presentation. Immediately after an intentional ingestion and in asymptomatic patients without spontaneous emesis, gastric aspiration should be carefully performed with a small nasogastric tube. Activated charcoal should be administered soon after ingestion (preferably within 1 hour) because it can limit further gut absorption and enhance elimination by interrupting enterohepatic or enteroenteric circulation [27]. Also, cholestyramine may interrupt enteric circulation and enhance elimination. Chlordecone and chlordane undergo enterohepatic circulation, and cholestyramine is indicated in symptomatic patients. In a controlled trial, cholestyramine was administered as 16 g per day to symptomatic factory workers exposed to chlordane. After 5 months, chlordane fecal elimination was shown to increase by 3.3 to 17.8 times, with neurologic symptoms improving as concentrations declined. Milk- and oil-based cathartics should be avoided because their high lipid solubility can enhance gut absorption. Hemodialysis is not effective in enhancing elimination of these chemicals because of their high volume of distribution and protein binding [52]. Hemoperfusion is probably of no benefit [52].

Organochlorine-induced seizures are managed with benzodiazepines and barbiturates. Phenytoin has not been demonstrated to be more effective as an anticonvulsant than barbiturates and it may actually increase the incidence of these seizures [53,54]. For uncontrolled status epilepticus, muscle paralysis and general anesthesia may be necessary. Aggressive seizure control is warranted to limit further development of CNS damage, metabolic acidosis, hyperthermia, rhabdomyolysis, and myoglobinuric renal failure.

Respiratory distress due to bronchospasm is managed with humidified oxygen and nebulized bronchodilators. Parenteral administration of adrenergic amines is not recommended because it may potentiate myocardial irritability. Early administration of steroids and prophylactic use of antibiotics for pulmonary aspiration have not been demonstrated to improve patient outcome. The early use of antibiotics may predispose to the selective growth of other bacterial organisms.

After appropriate decontamination, asymptomatic patients with an oral exposure can be observed for 6 hours and then discharged if their clinical status remains unchanged. Patients presenting with cardiovascular, CNS, or persistent respiratory manifestations should be admitted for further therapy and observation.

PYRETHROIDS

Pyrethrum is a collection of naturally occurring insecticide esters from the chrysanthemum flower. The pyrethrin I ester has the greatest insecticidal activity and is subject to rapid environmental degradation. To enhance its effectiveness in commercial use, synthetic alternatives known as pyrethroids were developed that are more resistant to decay. These compounds are present in consumer products, from flea and tick removers for pets to topical pediculicides.

Pharmacology

The pyrethroids (including pyrethrins) delay closure of the sodium channel during the end of depolarization, with resultant insect paralysis. Piperonyl butoxide is commonly added to commercial preparations to inhibit insects' ability to metabolize the pyrethroid and prolong activity. In mammals, these agents are relatively nontoxic because of the low concentrations and rapid mammalian metabolism. However, people who are allergic to ragweed may have hypersensitivity reactions to pyrethroids. The degree of this cross-sensitization has been reported to be as high as 46%. Pyrethroids have no effects on cholinesterase activity, and atropine and pralidoxime are not indicated in therapy.

Pyrethroids are readily absorbed from the GI tract. Dermal absorption varies depending on the type of agent and additive organic solvents. Systemic absorption is enhanced in the presence of petroleum distillates. These compounds are highly lipid soluble and largely metabolized by the mixed-function oxidase enzymes in the liver.

Clinical Toxicity

Poisoning from pyrethroids can result from inhalational, dermal, or oral exposures [42,44,55–57]. Nausea, vomiting, and diarrhea may occur after ingestion [44,57]. Neurologic manifestations and hypersensitivity reactions, including anaphylaxis, are the most common forms of systemic toxicity. Neurologic findings depend on the type and concentration of the pyrethroid and include paresthesias, muscle fasciculations, coma, and seizures [44,55,57]. Patients with an intentional ingestion of a mixture containing an organophosphate and a pyrethroid can present with predominant cholinergic manifestations [58].

Management

Treatment is very similar to that described for organochlorines (see previous discussion). GI decontamination may be appropriate, but there is no role for repeat-dose–activated charcoal and cholestyramine therapy because enterohepatic circulation has not been demonstrated for the pyrethroids. Hypersensitivity reactions, including anaphylaxis, should be managed with epinephrine, steroids, antihistamines, bronchodilators, and vasopressors, as indicated.

Asymptomatic patients with oral exposures can be observed for 6 hours and medically cleared of toxicity if their clinical status remains unchanged. Patients presenting with

cardiovascular, CNS, or persistent respiratory manifestations should be admitted for further therapy and observation.

ANTICOAGULANTS

Bishydroxycoumarin (dicumarol), the first anticoagulant, was isolated as the hemorrhagic agent in *sweet clover disease*, a bleeding disorder that resulted from the ingestion of spoiled clover silage. Numerous congeners, such as warfarin (3-α-acetonylbenzyl-4-hydroxycoumarin), have since been synthesized and used as a rodenticide. Typically, for the bait to be effective, the rodent must consume it for 3 to 10 days; however, continuous feeding for 21 days may be necessary to achieve 100% mortality. As rodents became increasingly resistant, warfarin derivatives were introduced and have supplanted warfarin. These "superwarfarins," or long-acting anticoagulants, include brodifacoum, difenacoum, and indanedione derivatives. The long-acting anticoagulants are 100 times more potent than warfarin and have a much longer half-life. Most anticoagulant rodenticide is packaged with cereal or other food products as bait, with the amount of rodenticide in the product varying from 0.025% to 0.005% per weight. Acute accidental or suicidal ingestion of a minimal amount of bait containing long-acting anticoagulants is unlikely to cause toxicity [59]. However, a "mouthful" of a long-acting anticoagulant ingestion in an adult human has been reported to cause significant coagulopathy [60–62].

Pharmacology

Warfarin and its derivatives are oxidized by mixed-function oxidases into inactive metabolites in the liver [63]. The plasma half-life of warfarin is 42 hours, with duration of action of 2 to 5 days [63]. The long-acting anticoagulants are concentrated in the liver and have extremely long half-lives; brodifacoum has a half-life of 120 days in dogs, 61 hours in rabbits, and 156 hours in rats [64–66]. The half-life of long-acting anticoagulants may be affected by the dose. The exact half-life of long-acting anticoagulants in humans is unknown, and because of significant interspecies variation, animal data cannot be extrapolated to humans. Case reports in human exposures have reported half-lives of 6 to 23 days for chlorophacinone and 16 to 39 days for brodifacoum [60,67–70]. Clinical coagulopathy may persist as long as 42 to 300 days [67–69,71–74].

These anticoagulants inhibit vitamin K 2,3-epoxide reductase and, to a lesser extent, vitamin K reductase. These enzymes are responsible for the cyclic regeneration of vitamin K [75,76]. Vitamin K is the active coenzyme responsible for activation of clotting factors II, VII, IX, and X, as well as anticoagulant factors protein C and protein S, by hepatic γ -carboxylation of the *N*-terminal glutamate residual of these proteins [75]. Once activated, vitamin K–dependent clotting factors can interact with calcium and phospholipids in the coagulation cascade [70]. Inhibition of vitamin K 2,3-epoxide reductase and vitamin K reductase depletes vitamin K and vitamin K–dependent clotting factors, resulting in coagulopathy and bleeding. The half-lives of vitamin K–dependent clotting factors are 7 hours for factor VII, 24 hours for factor IX, 36 hours for factor X, and 50 hours for factor II [63]. Because factor VII has the shortest half-life of the vitamin K–dependent clotting factors, increases in prothrombin time or international normalized ratio (INR) are not seen until 50% to 70% of factor VII is depleted. In a healthy person, this change occurs 24 to 48 hours after ingestion [59]. Clinical coagulopathy may not be evident for several days when the other vitamin K–dependent factors are also depleted, however [77,78].

Clinical Toxicity

The primary manifestation of poisoning is coagulopathy. The most common signs are cutaneous bleeding, soft-tissue ecchymosis, gingival bleeding, epistaxis, hematuria, and increased menstrual bleeding [61,79]. Gross hematuria, GI bleeding, hemoptysis, and peritoneal and diffuse alveolar bleeding may occur in patients with more serious poisoning [80–83]. Fatalities are uncommon and usually result from complications of intracranial hemorrhage [82,84].

Management

Gastric decontamination with activated charcoal should be initiated for acute ingestions. The most important laboratory studies are the prothrombin time and INR. Soon after an acute ingestion, values are expected to be normal; assays must be repeated at least 48 hours after exposure because of delayed coagulopathy [59]. Prophylactic vitamin K therapy can delay the onset of coagulopathy, but is not recommended as it may obscure the diagnosis and mandate prolonged coagulation profile monitoring, which might otherwise be unnecessary. Clotting factor analysis, particularly for factor VII, is a more sensitive and earlier indicator of coagulopathy [59]. Factor analysis does not offer more useful information in most patients with minimal ingestions, however. Occasionally, serum detection for warfarin and its derivatives has demonstrated unsuspected exposures in patients with coagulopathy of unknown cause [62,71]. In patients with coagulopathy, serial monitoring of warfarin derivative concentrations can assist in predicting the duration of coagulopathy and therapy [67].

The primary treatment of anticoagulant toxicity is vitamin K replacement [85,86]. Warfarin and its congeners have much less effect on human than on rat vitamin K reductase, thus allowing vitamin K rescue therapy for anticoagulant toxicity in humans. Because a single dose of vitamin K therapy cannot affect the prolonged toxicity of the long-acting anticoagulants, empiric vitamin K therapy is not recommended unless the patient has a coagulopathy. Vitamin K is not immediately effective in reversing coagulopathy; fresh-frozen plasma (FFP) administration is indicated in patients with significant bleeding diathesis (Table 141.3). Factor-specific concentrates have been demonstrated to decrease the time to correction of the INR in patients with a coagulopathy from warfarin toxicity faster than FFP [87]. The experience with these agents in the treatment of long-acting anticoagulant rodenticides, such as brodifacoum, is limited. Activated factor VII (FVIIa), FFP, and vitamin K have been used to treat brodifacoum toxicity [88,89]. In one of these instances, a product containing FVIIa and prothrombin complex concentrates (factor II, IX, and X) was used [88]. Some advantages of factor-specific concentrates over FFP include improved consistency in correction of the INR and decreased amount of fluid administered.

Only vitamin K_1 (phytonadione) should be used because the other forms (K_2, K_3, and K_4) are ineffective in the treatment of anticoagulant toxicity. Vitamin K_1 can be administered orally, subcutaneously, intramuscularly, and intravenously. Intravenous administration has been associated with anaphylactoid reactions and death [90–92]. Furthermore, it offers no real advantage over other routes of administration. Intramuscular injection may cause hematoma formation in patients with coagulopathy. Subcutaneous administration of vitamin K_1 is safe and effective. Oral vitamin K_1 may be simpler and just as efficacious [93]. The oral vitamin K_1 dose required to reverse coagulopathy is variable, but typically ranges from 100 to 300 mg per day, divided three to four times per day [61,66,80]. The amount

TABLE 141.3

TREATMENT GUIDELINES FOR COAGULOPATHY FROM LONG-ACTING WARFARIN-LIKE RODENTICIDES IN PATIENTS WITH NO UNDERLYING RISKS FOR THROMBOEMBOLISM

Active bleeding, major and life threatening

1. Factor replacement
   Fresh-frozen plasma (15 mL/kg)
   and
   Factor-specific concentrates, such as prothrombin complex concentrates (50 units/kg) or activated factor VII
   and
2. Vitamin K_1 intravenous (adult 10 mg, pediatrics 100 µg/kg by slow infusion)
3. Packed red blood cells for significant bleeding (i.e., anemia and hypotension)

No active bleeding and international normalized ratio (INR) ≥ 4.0

1. Vitamin K_1 intravenous (adult 10 mg, pediatrics 100 µg/kg by slow infusion)

Adapted from Leissinger CA, Blatt PM, Hoots WK, et al: Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. *Am J Hematol* 83:137–143, 2008; and Watt BE, Proudfoot AT, Bradberry SM, et al: Anticoagulant rodenticides. *Toxicol Rev* 24:259–269, 2005.

of vitamin K therapy must be titrated to clinical response, however. The duration of vitamin K therapy and coagulopathy is also highly variable, ranging from 40 to 300 days. When the patient's INR has remained normal for several days after stopping the treatment, vitamin K therapy can be discontinued. The trend of the patient's concentration of clotting factors during this period may assist the determination of this clinical endpoint. Various methods have been proposed to decrease the duration of coagulopathy, including administration of hepatic enzyme inducers such as phenobarbital [64,66]. There is no good evidence to support any of these therapies, however.

STRYCHNINE

The use of strychnine as a pesticide dates back to the sixteenth century, when an extract of the Filipino St. Ignatius bean (*Strychnos ignatii*) was introduced as a rodenticide in Europe. Strychnine was used as a tonic, cathartic, and aphrodisiac as late as 1970, and resulted in numerous deaths [94]. It is also found as an adulterant in illicit drugs, such as cocaine and heroin. The only "legitimate" uses of strychnine today are as a pesticide and in research study of neural transmission [94,95].

Pharmacology

Strychnine is rapidly absorbed through the nasal mucosa and orally in the small intestine. It undergoes hepatic oxidative transformation to unknown metabolites [96], and only 10% to 20% is excreted unchanged in the urine within 24 hours. The half-life of strychnine in humans is 10 to 16 hours, and the volume of distribution is 13 L per kg [97,98].

Strychnine competitively antagonizes postsynaptic glycine receptors at the spinal cord and, to a lesser degree, at the brain stem, cerebral cortex, and hippocampus [95,99,100]. Strychnine-binding sites overlap, but are distinct from glycine-binding sites at the glycine receptor [100,101]. Glycine receptors at the cerebral cortex and hippocampus are of a subtype insensitive to strychnine and are minimally affected [95]. The action of glycine is similar to that of γ-aminobutyric acid in that it enhances chloride ionic channel conduction, resulting in hyperpolarization of postsynaptic membrane and an increased threshold for neurologic transmission [95,102]. The highest concentration of glycine receptors is found at the ventral horn motor neurons in the spinal cord [102]. Glycine antagonism reduces neuromuscular inhibition, including reciprocal inhibition between antagonistic muscles, resulting in contraction of both flexor and extensor muscle groups [103]. The pharmacologic effect of strychnine is quite similar to that of tetanus toxin, which inhibits the release of glycine at postsynaptic neurons in the spinal cord [102,104].

Clinical Toxicity

The onset of toxicity is usually within 15 to 30 minutes of exposure. The lethal dose in adults is typically 50 to 100 mg, but it may be as little as 5 to 10 mg in children [94,105]. Diffuse muscle contractions and spasms are the primary manifestations of strychnine toxicity. Facial muscle spasms result in risus sardonicus (the "sardonic smile") and trismus. Opisthotonos, abdominal muscle contractions, and tonic movements of the extremities may resemble convulsions. Because glycine has limited effects in the higher CNS centers, seizures are unlikely and mental status is normally preserved until the patient is hypoxic or moribund [94,105]. The extensor muscles appear to be more affected than the flexor muscles because they are the antigravity muscles and generally stronger [94,105]. Muscle contractions can be triggered or amplified by any stimulations, including auditory, tactile, and visual stimuli, and may lead to lactic acidosis, rhabdomyolysis, and hyperthermia [103,106]. Respiratory depression results from sustained chest and diaphragmatic muscle contractions and brain-stem depression. Death is related to respiratory depression, anoxia, and complications from significant muscle contractions [97,105]. The clinical manifestations of strychnine toxicity differ from tetanus infection in that the onset of symptoms in tetanus infection is more gradual and the duration of illness is more prolonged [104].

Management

Securing the airway, assisting breathing, and maintaining the circulatory system are the immediate goals in symptomatic patients. Electrolytes, acid–base changes, oxygenation saturation, renal function, urine output, and temperature must be monitored carefully in any symptomatic patient. GI decontamination should be performed in any case of suspected strychnine ingestion. Enhanced elimination by urinary manipulation has no effect because of minimal renal elimination [96]. Hemodialysis or charcoal hemoperfusion is ineffective because of the large volume of distribution.

Termination of muscle contractions prevents or reverses lactic acidosis, rhabdomyolysis, hyperthermia, and respiratory depression. Benzodiazepines are the initial agents of choice in attenuating musculoskeletal signs and symptoms [107–109]. Benzodiazepines enhance γ-aminobutyric acid effects in the spinal cord and may displace strychnine binding to glycine receptors [100,110,111]. Barbiturates also are reported to be useful in the treatment of strychnine toxicity. These agents may not be completely effective in patients with severe strychnine poisoning, however, and other agents such as propofol and adjunct nondepolarizing neuromuscular blockade may be required [98,105]. Strychnine toxicity usually resolves within

12 to 24 hours [96,103,112]. Supportive therapy should be continued until the patient is asymptomatic.

SODIUM MONOFLUOROACETATE

Sodium monofluoroacetate is frequently referred to as "compound 1080," the number assigned to the compound during its initial development. It is the primary toxic constituent in the South African gifblaar (*Dichapetalum cymosum*), but it is also present in other plants in South America and Australia. Fluoroacetate is highly toxic to all mammals, and its use was banned in the United States in 1972 because of human fatalities and indiscriminate extermination of nontarget species. The congener sodium fluoroacetamide (compound 1081), also used as a pesticide, has mechanisms and effects similar to those of fluoroacetate. Prior to compound 1080's ban in the United States in 1972, it was mostly used in livestock protection collars (tubular collars filled with pesticide, which is released when bitten by predators).

Pharmacology

Fluoroacetate appears to be minimally absorbed through skin but rapidly absorbed from the GI tract. It is metabolized to fluorocitrate in the tricarboxylic acid (TCA) cycle, with 12% of the ingested dose excreted in the urine [113]. In animals with relative resistance to monofluoroacetate, a hepatic defluorination system cleaves the carbon–fluoride bond to detoxify the compound [114].

Fluoroacetate is structurally similar to acetate and is incorporated into the TCA cycle with the assistance of acetyl coenzyme A. Fluoroacetate combines with citrate to form fluorocitrate in the TCA cycle [115]. Fluorocitrate inhibits aconitase and succinate dehydrogenase and disrupts the TCA cycle, halting cellular respiration and causing cell death [108,115,116]. Organs with high metabolic demands, such as the brain and heart, are immediately affected [117]. The lethal dose of sodium monofluoroacetate is 2 to 10 mg per kg [116].

Clinical Toxicity

The onset of poisoning occurs within 1 to 2 hours of exposure. Nausea and vomiting are followed by CNS and cardiovascular manifestations, which are the primary toxicities in humans [116,117]. The patient may present with agitation, lethargy, seizures, and coma [117–119]. Cardiovascular manifestations include tachycardia, premature ventricular contractions, ST-segment abnormalities, hypotension, ventricular tachycardia, and ventricular fibrillation [116]. Acute renal failure may be related to hypotension, rhabdomyolysis, and the direct toxic effects of monofluoroacetate on the kidney [117]. Fatality is related to CNS and cardiovascular toxicities [120,121]. Laboratory abnormalities include significant metabolic acidosis and hypocalcemia from the fluoride ion.

Management

General supportive measures are paramount and aimed at maintaining the airway, breathing, and circulation. Activated charcoal should be administered in all suspected oral exposures presenting within 1 to 2 hours after ingestion. Seizures should be treated with benzodiazepines or barbiturates. Hypocalcemia and prolonged QTc intervals may require calcium and magnesium supplementation. Various treatments have been tested in animals [122,123]. The most useful agent appears to be glyceryl monoacetate, which provides excess acetate as a substrate for the TCA cycle [122,124]. The clinical use of glyceryl monoacetate remains unproven, however.

ALUMINUM AND ZINC PHOSPHIDES

Aluminum and zinc phosphides are highly toxic insecticides and rodenticides commonly used as solid fumigants and grain preservatives. They are considered to be ideal pesticides for grain preservation because of the simplicity of application, low cost, and high efficacy without grain contamination. Although highly restricted in the United States, aluminum phosphide is widely available and commonly used for home grain storage in Asia and the Middle East. Typically, each pellet contains 3 g of 56% aluminum phosphide [125]. Aluminum phosphide has become one of the most common suicidal agents in India and other developing countries [10,125–128]. As little as 0.5 g can be fatal to an adult [129]. Phosphides are widely used in grain freighters and have emerged as the major maritime occupational health hazard [130]. Phosphine is slowly liberated when phosphides react with moisture in the environment.

Pharmacology

Phosphides react with water to form phosphine; the reaction is exothermic and it may be accelerated in the acidic environment of the stomach [126,131]. Phosphine is then readily absorbed in the stomach. Phosphine itself can also be absorbed through the lungs. There is limited information on the pharmacokinetics and metabolism of phosphine, although it is known to be partly eliminated through the lungs [131].

The exact mechanisms of toxicity have not been elucidated; the most likely mechanism is related to noncompetitive inhibition of cytochrome C oxidase. Also, phosphine increases the production of superoxide dismutase and lipid peroxidation [132]. As a cellular toxin, phosphine has deleterious effects on multiple organ systems, particularly organs with high metabolic demands.

Clinical Toxicity

Inhalation of phosphine gas results in immediate eye and mucus membrane irritation and early onset of pulmonary symptoms [126,129]. Oral ingestion of phosphides causes profound GI symptoms, including nausea, vomiting, and abdominal pain [125,129]. In these instances, esophageal lesions, such as ulcers, perforations, and strictures, can occur and they are typically associated with the ingestion of undiluted pellets [133,134]. Respiratory symptoms include cough, dyspnea, and chest tightness. Pulmonary edema and respiratory failure may be delayed for several hours after oral exposure to phosphides [125,135,136]. Hypotension and shock are expected within 6 hours in serious exposures. Fatalities are related to cardiovascular collapse from vasodilation and myocardial damage [137–139]. Various electrocardiographic changes have been reported, including ST-segment elevation and depression, QRS prolongation, bundle-branch blocks, atrioventricular nodal blockade, and supraventricular and ventricular tachycardia [140–142]. CNS effects lead to headache, lethargy, and encephalopathy [134]. Other manifestations include severe metabolic acidosis, hepatitis, and renal failure [137]. Mortality rates vary from 38% to 77% in suicidal ingestions [125,129,135,138,139].

Management

The patient should be immediately removed from the contaminated environment after the rescuer is adequately protected. Airway, breathing, and circulatory support are important in the immediate management. Activated charcoal should be mixed with sorbitol or magnesium citrate, rather than plain water, to reduce further liberation of phosphine in the GI tract [126]. Careful lavage with sodium bicarbonate (3% to 5% solution) or antacid has been advocated [143], but has not been adequately studied.

Cardiac monitoring and electrocardiography should be performed in suspected phosphine toxicity. Respiratory status should be monitored by continued clinical evaluation. Hypo- and hypermagnesemia have been reported with aluminum phosphide poisoning. Chest radiography, pulse oximetry, and arterial blood gases should be obtained as clinically indicated. The diagnosis may be suggested from a decaying fish odor released by substituted phosphines and diphosphines [126]. Silver nitrate–impregnated paper blackens in the presence of phosphine in the gastric fluid [144].

There is no antidote for phosphine poisoning. The mainstay of therapy is supportive care. Although intravenous magnesium therapy has been successful in treating various dysrhythmias [145–149], it has not been uniformly effective [150]. Magnesium therapy in phosphide poisoning should be considered in patients with dysrhythmias or hypomagnesemia.

METHYL BROMIDE

Methyl bromide (CH_3Br) is a colorless halogenated hydrocarbon gas primarily used as a fumigant for the control of nematodes, insects, rodents, fungi, and weeds. Methyl bromide has become one of the most widely used pesticides in the United States and worldwide since the abandonment of chlordane and acrylonitrile as fumigants [151,152]. Because methyl bromide causes ozone depletion in the stratosphere, the Montreal Protocol restricted its use in most developed countries since 2005. The United Nations proposed complete elimination of methyl bromide use worldwide by 2015. Methyl bromide was particularly popular in the food industry because it is extremely effective, is able to diffuse into any empty spaces, and does not leave any residues after proper ventilation. Space fumigation of fruits and tobacco can be performed in an airtight (fumigation) chamber. For soil fumigation, methyl bromide can be applied underground and sealed with an overlying tent or polyethylene cover. For structural fumigation, gas-proof tarpaulins are applied over the structure before the application of methyl bromide [153]. Methyl bromide is still used for the manufacture of chemicals such as aniline dyes. It has a musty and chloroform-like odor at high concentrations, but it is odorless at lower, but still very toxic, concentrations [154]. Because methyl bromide is heavier than air, it is particularly dangerous in an enclosed environment. Inadvertent exposures from accidents or inadequate ventilation have caused significant toxicities and fatalities [120,151,155–157].

Pharmacology

Methyl bromide is primarily absorbed through the lungs. Cutaneous absorption is minimal. Methyl bromide easily penetrates and is retained in cloth, rubber, and leather [153,158]. It is eliminated unchanged in the lungs, but a small proportion is metabolized to 5-methylcysteine and inorganic bromide; these are excreted in the urine [159].

The mechanism of toxicity is probably related to the methylation of sulfhydryl groups in different intracellular enzymes, as in heavy metal intoxication. Low concentrations of bromide can be detected in the serum after significant exposure to methyl bromide, but they do not correlate well with toxicity [151]. The symptoms of methyl bromide toxicity are distinctly different from those of bromide salt toxicity [160].

Toxic effects primarily involve the central nervous and pulmonary systems [151]. Although exposures to concentrations of 2,000 ppm or greater may produce immediate CNS depression and respiratory failure, symptoms may be delayed for 1 to 6 hours or longer with exposure to lower concentrations [153,157]. The current Occupational Safety and Health Administration permissible exposure limit for methyl bromide is 20 ppm [161].

Clinical Toxicity

Patients with mild toxicity may manifest dizziness, headache, confusion, weakness, nausea, vomiting, and dyspnea [120]. Initial or mild symptoms are frequently dismissed as viral symptoms [156]. Skin irritation and burns commonly underlie clothes and rubber gloves, where the methyl bromide gas is trapped [158]. After a significant exposure, the patient may present with tremor, myoclonus, and behavioral changes [121,162,163]. Severe toxicity may result in bronchitis, pulmonary edema, convulsions, and coma [151,157]. Fatality is related to pulmonary and CNS toxicities, although damage to different internal organs has been demonstrated [151,160,164]. Prolonged exposure to low concentrations of methyl bromide may cause subacute neurologic effects, such as headaches, confusion, behavioral changes, visual disturbance, and motor and sensory deficits [160,165–167]. Residual neurologic deficits may remain after significant acute or chronic exposure [160,164,168].

The essential laboratory studies in patients with methyl bromide intoxication are arterial blood gas or pulse oximetry monitoring. Chest radiography is useful in evaluating patients with pulmonary symptoms. Serum bromide concentrations may confirm exposure, but do not correlate with the severity of exposure. Serum bromide concentrations varied from 4.0 to 65.6 mg per dL in methyl bromide fatalities [151,160,169]. When the serum bromide concentration is significantly elevated, an elevated chloride concentration may be observed because of cross-reactivity in the analytical method [168].

Management

Treatment consists of supportive therapy, particularly of the airway, breathing, and circulation. Because methyl bromide is a gas, GI decontamination is not relevant. Clothing should be completely removed and the skin washed with soap and water to eliminate potential methyl bromide residues. Various compounds with sulfhydryl groups, such as dimercaprol and *N*-acetylcysteine, have been suggested as potential antidotes [158,162], but have not been demonstrated to be effective.

N,N-DIETHYL-M-TOLUAMIDE

N,*N*-diethyl-*m*-toluamide (diethyltoluamide, or DEET) was initially synthesized in 1954 and marketed as an insect repellent. Currently, DEET is the most effective and one of the most widely used insect repellents [170]. Use of DEET continues to increase with increasing public concern over Lyme disease and West Nile virus transmission. The concentration of DEET in the various products varies from 5% to 100%.

Pharmacology

DEET is well absorbed through the skin, with 48% of the applied dose absorbed within 6 hours. The plasma concentration peaks 1 hour after dermal application [171]. DEET is primarily metabolized in the liver, and 70% of the absorbed dose is excreted as metabolites within the first 24 hours. Another 10% to 15% is excreted unchanged in the urine [171]. DEET and its metabolites may accumulate in the fatty tissue, particularly after repeated applications.

The mechanism of DEET toxicity is unknown. Animals develop CNS symptoms similar to those reported in humans. Most reports of human poisoning involve children, likely because children absorb a higher ratio of DEET relative to their body weight. The initial theory suggested that patients with ornithine-carbamoyltransferase deficiency might be particularly susceptible to DEET toxicity [172]. However, recent reports have refuted this theory [173,174].

Clinical Toxicity

DEET may cause toxicity that is limited to skin irritation, contact dermatitis, skin necrosis, and urticaria [174–176]. Anaphylactic reactions have occasionally been reported with cutaneous application [176]. Manifestations of systemic poisoning vary from anxiety to behavioral changes, tremors, lethargy, ataxia, confusion, seizures, and coma [172–174,177–179]. Almost all of these case reports are related to application of concentrated DEET preparations or repeated application of lower concentration preparations [140,172,173,180].

Management

Treatment is largely supportive. Patients with dermal exposure should have their skin washed with soap and water to prevent further systemic absorption. Seizures may be treated with benzodiazepines. Neurologic workup may be required in many patients. The symptoms of DEET toxicity should be distinguished from those of Reye syndrome [172]. There is no antidote, and extracorporeal removal procedures are not helpful. Measures to prevent DEET toxicity may be the most important treatment. These include avoidance of concentrated DEET preparations. Products containing 20% to 30% DEET are adequate and safer than those with higher concentrations; concentrations of 10% or less are recommended for children. DEET should be applied only to exposed skin. An additional agent, such as permethrin, can be applied to clothing and may decrease the need of DEET [170]. The skin should be washed with soap when the insect repellent is no longer required, and the number of repeat applications should be limited.

PENTACHLOROPHENOL

Pentachlorophenol was first synthesized in 1841 and first used as a pesticide in 1936 [141]. It is primarily used as a wood preservative, however. Unlike other types of pesticide toxicity in adults, pentachlorophenol poisoning usually results from occupational exposure [142]. Occupational exposures to pentachlorophenol at wood-treating facilities frequently result from improper ventilation and inadequate engineering controls. Low-concentration, prolonged exposures to pentachlorophenol have been reported in log home residents from pentachlorophenol-treated wood [181]. Epidemics of infant poisoning have resulted from diapers improperly laundered with pentachlorophenol-containing antimicrobial soaps [182].

Pharmacology

Pentachlorophenol can be absorbed by the respiratory, oral, and dermal routes, although pulmonary absorption is the most efficient route. The volume of distribution is 0.35 L per kg and the pK_a is 5.0 [183]. Pentachlorophenol is primarily (74%) eliminated unchanged in the urine. A small proportion is oxidized to chlorohydroquinone, which is then eliminated in the urine. After a single oral exposure, the plasma half-life of pentachlorophenol is 27 to 35 hours [183]. Because of the low pK_a and significant renal elimination, pentachlorophenol elimination can be enhanced by urinary alkalinization [184].

The mechanism of toxicity of pentachlorophenol is similar to that of dinitrophenol: these agents uncouple oxidative phosphorylation by interfering with electron transport between flavoprotein and cytochrome P450.

Clinical Toxicity

Acute exposure results in headache, diaphoresis, nausea, vomiting, weakness, abdominal pain, and fever. With severe toxicity, significant hyperthermia (up to 108°F or 42.2°C), coma, convulsions, cerebral edema, and cardiovascular collapse may occur [141,185–187]. Laboratory studies may reveal a respiratory alkalosis and metabolic acidosis from significant exposures. Chronic exposures to pentachlorophenol have been reported to cause aplastic anemia, intravascular hemolysis, and pancreatitis [188–190]. Chloracne has also been reported from these exposures because of dioxin contamination in the product [186].

Management

Initial treatment includes oxygen supplementation, airway support, fluid resuscitation, and cardiac monitoring. Core temperature should be frequently monitored, and external cooling should be initiated immediately for significant hyperthermia. Seizures should be treated immediately with benzodiazepines or barbiturates to prevent further temperature increase and rhabdomyolysis. Fluid administration should be adequate to maintain a urine output of 1 to 2 mL per minute. Gastric decontamination (see Chapter 117) should be performed for oral exposure. The skin should be decontaminated with soap and water. Urinary alkalinization should be considered in patients with significant pentachlorophenol toxicity, although its clinical efficacy remains unproven [184].

PARAQUAT

Paraquat (1,1-dimethyl,4,4-bipyridyl dichloride) was developed in 1882 and for many years was used as an oxidation–reduction indicator. An electron donation to the compound forms a blue free radical; hence, paraquat was commonly called *methyl viologen*. The herbicidal properties of paraquat were discovered in 1955, and it was marketed as an herbicide in 1962. Today, paraquat is most commonly used as a nonselective contact herbicide in many countries. Paraquat can be applied safely when used according to the manufacturer's guidelines [191]. Typically, it is available as a 10% to 30% concentrated solution for agricultural use or as a 5% powder for domestic use. Once diluted, paraquat has limited absorption through the skin [192] and by aerosolization into the

respiratory system [193]. Paraquat is naturally inactivated in the soil and leaves little active residue in the environment. Despite its many desirable properties, however, the consequences of ingesting concentrated paraquat products are deadly. The median lethal dose of paraquat is 3 to 5 g in adults [194]. As little as a mouthful (10 to 15 mL) of a 20% solution of paraquat is fatal. Paraquat ingestion is a prevalent method of suicide in countries such as Taiwan, Japan, Malaysia, the West Indies, and Samoa [10].

Pharmacology

Although oral exposure to paraquat is the most common route of toxicity, less than 5% of the ingested amount is actually absorbed [195]. Any recent food ingestion may decrease the amount of systemic absorption. The peak plasma concentration is reached within 1 to 2 hours after ingestion. Paraquat is almost completely eliminated unchanged by the renal system [195]. Plasma paraquat concentrations decline rapidly after peak absorption because of tissue distribution. The terminal plasma half-life of paraquat is 12 hours with normal renal function, but it may be as long as 120 hours as renal function deteriorates [196]. The volume of distribution of paraquat estimated from kinetic study in one patient is 2.75 L per kg. Paraquat is particularly sequestered in the lungs and kidneys [195].

Dermal absorption of paraquat is minimal unless the exposure is prolonged with concentrated solutions [192]. Aerosolized paraquat particles have a diameter greater than 5 μm and do not reach the lower respiratory tree [193]. Concern about paraquat absorption from smoking marijuana is unfounded because much of the paraquat is pyrolyzed during the smoking process [197]. Paraquat toxicity from marijuana smoking has not been reported.

The primary organ of toxicity is the lung because of selective accumulation of paraquat. Paraquat is actively transported into type I and II alveolar cells through an existing transport system for endogenous polyamines. Paraquat and polyamines share a common structural property: they have two positively charged quaternary nitrogen atoms separated by a distance of 6 to 7 nm [198]. Diquat, another related herbicide with different structural features, is not selectively taken up and does not cause pulmonary toxicity [198,199]. Inside the cell, paraquat undergoes a single-electron reduction into paraquat free radical. This free radical reacts with oxygen to form superoxide free radicals, which then deplete nicotinamide adenine dinucleotide phosphate, leading to lipid peroxidation and subsequent cellular destruction [200,201]. Also, this mechanism of action is responsible for the phytotoxic property of paraquat. There is also evidence for direct inhibition of electron chain transfers in mitochondria [200].

Clinical Toxicity

The onset and severity of poisoning is largely determined by the amount of exposure. Patients who ingest more than 40 mg per kg usually die within hours to a few days [202]. These patients experience multiple organ failure, including acute respiratory distress syndrome, cerebral edema, myocardial necrosis, and hepatic and renal failure [202–205]. Death can be dramatic and may occur even before the development of significant chest radiographic abnormalities [202]. Patients who ingest 20 to 40 mg per kg of paraquat are most likely to die from pulmonary fibrosis, which progresses after a few days to a few weeks [206,207]. Ingestion of less than 20 mg per kg may lead to mild toxicity [202,206].

Paraquat is extremely corrosive to mucus membranes, and patients frequently complain of pain in the mouth, throat, esophagus, and abdomen [203,206]. The absence of significant ulcerations in the esophagus or stomach within the first 24 hours of exposure is a good prognostic indicator [203]. The development of renal failure is a poor prognostic indicator [196,203,208]. This phenomenon cannot be fully explained by the decreased elimination of paraquat in the body because most of the paraquat dose is eliminated within the first 24 hours, even in the setting of renal failure [196,209]. Conversely, renal failure may signify a large paraquat exposure. Almost all patients with renal failure from paraquat have significant pulmonary toxicity, but there are occasional reports of renal failure without significant pulmonary toxicity [205]. The prognosis for a patient with paraquat ingestion can be determined by the measurement of plasma paraquat concentration and its relation to time of ingestion [210]. The nomogram initially was presented by Proudfoot et al. [211] and subsequently refined by Hart et al. [210]. The availability of paraquat measurements depends on regional practice because the laboratory analysis is not routine. Although it is generally accepted that paraquat is not absorbed through the skin, it can be corrosive to the skin and nails [192]. Occasionally, dermal absorption and systemic toxicity may occur from prolonged exposure or exposure to concentrated products [212].

Management

It is critical to prevent systemic absorption of paraquat. Once ingested, it is rapidly absorbed and sequestered, frequently leading to death [205]. GI decontamination should be performed in any suspected paraquat ingestion. Orogastric lavage should be performed if the ingestion is within 1 to 2 hours. Fuller's earth (1 to 2 g per kg) or activated charcoal should be administered with a cathartic agent as soon as possible to bind any residual paraquat in the GI tract [213–215]. Multiple doses of oral adsorbents should be continued until there is evidence of adsorbent in the stool. This is done to prevent desorption of the paraquat. Any dermal exposure should be thoroughly washed with soap. Plasma and urine analytical methods to detect paraquat are useful to confirm the diagnosis and assess the prognosis; they are generally not useful in direct management of the patient. A rapid qualitative screen for paraquat exposure may be performed by the addition of sodium dithionite to urine under alkaline condition, however. A change in color to blue confirms paraquat's absorption [216]. Furthermore, prognosis may be predicted by the degree of color change: dark blue for poor prognosis and light blue for moderate-to-severe poisoning [217].

The treatment of paraquat toxicity consists of supportive care, particularly respiratory monitoring and support. Chest radiographs, judicious administration of supplemental oxygen, and monitoring for acute respiratory distress syndrome and impending respiratory failure are important in patients with significant exposure. Excessive oxygen supplementation may increase the formation of paraquat free radicals and worsen pulmonary toxicity [218]. Supplemental oxygen should be administered only when it is necessary and should be maintained at the minimal required level.

Experimental therapies for paraquat toxicity have been formulated using various strategies [200,208]. Forced diuresis does not have significant effects on paraquat elimination. Hemodialysis and charcoal hemoperfusion can increase elimination. In an animal model, the institution of charcoal hemoperfusion within 2 hours after paraquat ingestion decreased the fatality rate [219], and institution of hemoperfusion 2 hours after paraquat administration did not alter the paraquat concentration in the central compartment [220,221]. Clinically,

hemodialysis, charcoal hemoperfusion, and continuous arteriovenous hemofiltration have not altered mortality rates. There are significant limitations in applying extracorporeal procedures. Because the volume of distribution of paraquat is relatively large and paraquat is rapidly sequestered into tissue compartments, extracorporeal removal must be performed during peak absorption (within 2 hours after ingestion) to significantly decrease the paraquat body load. Because most patients present a number of hours after ingestion and the logistics of extracorporeal removal typically translate into an additional 1- to 2-hour delay, the amount of paraquat removed in most instances is insignificant.

Immunotherapy with monoclonal antibody fragments (Fab, Fv) against paraquat or against the active transport mechanism in the cells is intriguing [222,223]. More research is required to assess the value of this therapy, however. Various agents such as putrescine and spermidine [224,225] and β-adrenergic receptor blockers have been demonstrated to prevent active transport of paraquat into lung tissues but failed to provide any benefits in vivo.

Various antioxidants and free radical scavengers, such as vitamins C and E [201,208,226], deferoxamine [227], superoxide dismutase [228], clofibrate [208], selenium [229], glutathione peroxide, and *N*-acetylcysteine [230,231], have been tested against paraquat toxicity. To date, there has been no or insignificant improvement in animal models. A recent study using inhaled nitric oxide in rats demonstrated benefits in preventing pulmonary injuries and survival. Several studies have demonstrated increased patient survival with corticosteroids and cyclophosphamide therapy [232–238]. The use of methylprednisolone and cyclophosphamide to limit the acute inflammatory response from paraquat toxicity appears to decrease mortality in patients with moderate-to-severe poisoning from ingested paraquat on the basis of prospective controlled trials [237,238]. In a randomized-controlled trial, paraquat-poisoned patients with a predicted mortality of 50% or greater and less than 90% and treated with pulse-dose methylprednisolone and cyclophosphamide (Table 141.4) were less likely to die at 6 weeks than those who did not receive the treatment (mortality rate: 5/16, 31.3% vs. 6/7, 85.7%) (Table 141.5) [237]. All patients received GI decontamination and two sessions of charcoal hemoperfusion within 24 hours of hospitalization, which were completed prior to the initiation of the pulse-dose therapy. Methylprednisolone and cyclophosphamide do not appear to affect the mortality rate in patients with mild and fulminant paraquat poisonings [217,236]. Cyclophosphamide can cause a transient leukopenia (WBC < 3,000 per μL) in patients treated with the protocol [233,237]. Additional clinical trials at other centers are needed to verify that pulse-dose therapy with methylprednisolone and cyclophosphamide improves survival in patients with paraquat toxicity.

Other agents that may alter pulmonary fibrosis, such as colchicine [239], nonsteroidal anti-inflammatory agents, collagen synthesis inhibitors [240], and angiotensin-converting enzyme inhibitors [241], also require further study. Niacin, which increases nicotinamide adenine dinucleotide phosphate synthesis, has some protective effects in rats, but it is unclear if it is applicable to human toxicity [242].

Early lung transplantation has been unsuccessful because of toxicity to the transplanted lung from paraquat distributing from tissue stores [243,244]. A successful case of lung transplantation was performed in a patient 44 days after paraquat poisoning, however [245].

TABLE 141.4

TREATMENT GUIDELINES FOR PULSE-DOSE METHYLPREDNISOLONE AND CYCLOPHOSPHAMIDE IN PATIENTS WITH PARAQUAT TOXICITY [237][a]

Initial pulse-dose therapy
Cyclophosphamide 15 mg/kg/d administered as an infusion in 200 mL D5NS over 2 h for 2 d
Methylprednisolone 1 g/d administered as an infusion in 200 mL D5NS over 2 h for 3 d

After initial pulse-dose therapy
Dexamethasone 5 mg IV every 6 h until $PaO_2 \geq 80$ mm Hg or death

If $PaO_2 < 60$ mm Hg after initial pulse therapy, repeat pulse-dose therapy with
Methylprednisolone 1 g/d administered as an infusion in 200 mL D5NS over 2 h for 3 d, and

If WBC > 3,000 per μL at > 2 wk after initial pulse-dose therapy, add
Cyclophosphamide 15 mg/kg/d administered as an infusion in 200 mL D5NS over 2 h for 1 d

[a]Initiated after gastrointestinal decontamination and two sessions of charcoal hemoperfusion within 24 h of ingesting paraquat in patients with moderate-to-severe toxicity.

DIQUAT

Diquat (1,1′-ethylene-2,2′-dipyridylium ion) is a contact herbicide with action and structure similar to that of paraquat. Diquat and paraquat liberate hydrogen peroxide and oxygen free radicals, resulting in toxicity to plants and animals. The use of diquat is more limited and hence results in fewer intoxications than paraquat. Diquat is often formulated with paraquat.

Pharmacology

The kinetics of diquat are unknown in humans. In animal models, less than 10% of the oral dose is absorbed. More than 90% of the absorbed dose is eliminated unchanged by the kidneys. There are no known metabolites of diquat.

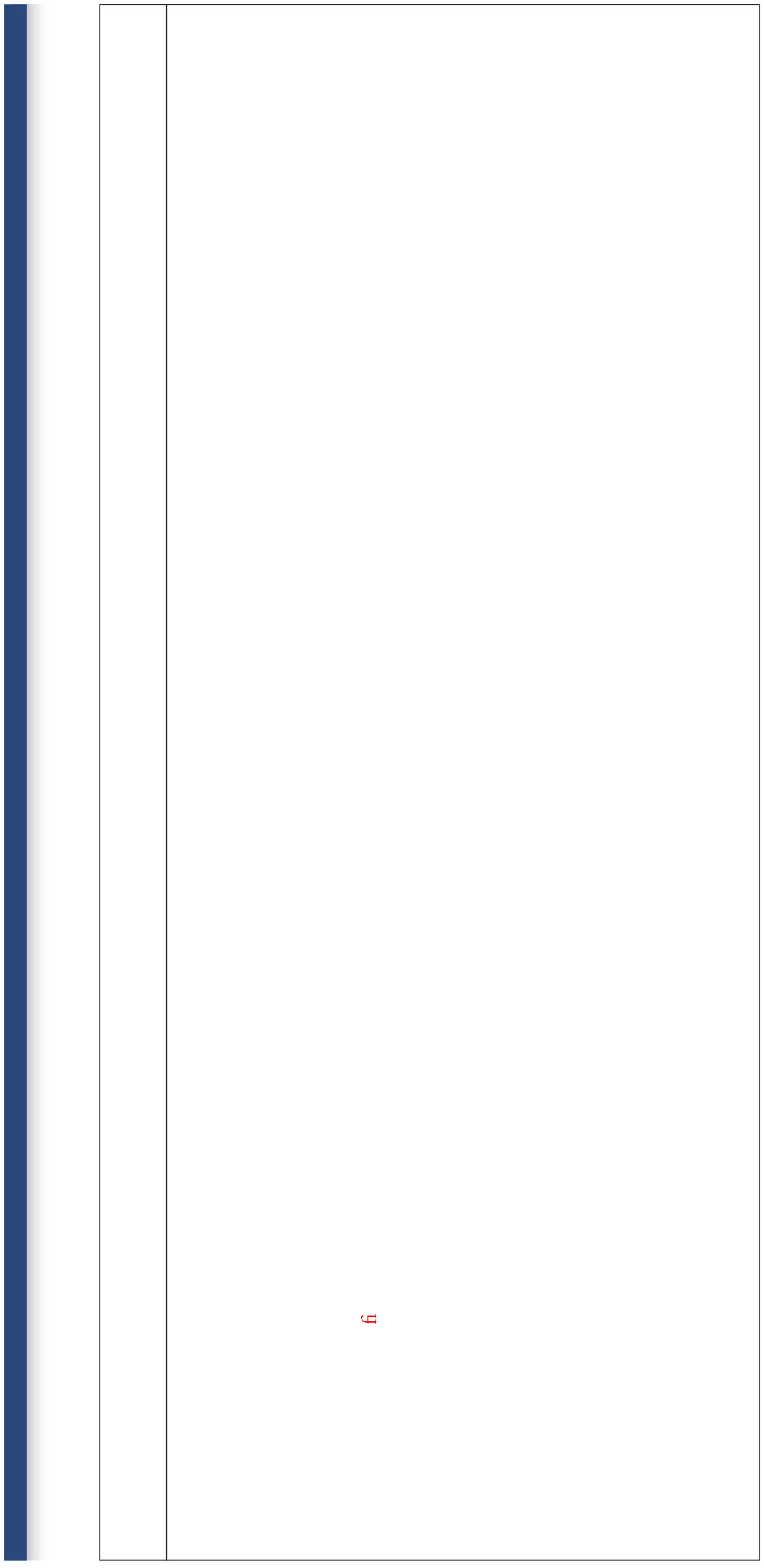
Although diquat is less toxic than paraquat, human fatalities have been reported with ingestion of 20 to 50 mL of a 20% solution [246]. Similar to paraquat, diquat causes multiple organ damage. Diquat normally spares the pulmonary system, however [246]. This is because diquat is not actively transported to and concentrated in the alveolar cells of the lungs [199].

Clinical Toxicity

Symptoms of diquat toxicity may be delayed several hours to 2 days [247]. Vomiting, abdominal pain, GI tract erosions, and paralytic ileus are common manifestations of toxicity [246,248,249]. Acute renal failure may be related to hypovolemia and the direct toxic effects. The effects of diquat on the CNS may result in lethargy, seizures, and coma [248,250]. Brain-stem infarctions may be specific to diquat toxicity. All patients who die have significant CNS manifestations before cardiovascular collapse [246,249].

Management

Treatment is largely supportive and similar to that for paraquat. Gastric lavage should be performed for any potential diquat ingestion within 2 hours. Fuller's earth or activated charcoal should be administered as soon as possible. Hemodialysis or



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hemoperfusion has not been demonstrated to be effective for the treatment of diquat toxicity [246,249,251,252].

CHLOROPHENOXY HERBICIDES

Chlorophenoxy herbicides are used to control broad-leaf weeds and woody plants. They exert their effects by mimicking the action of auxins (plant growth hormones) and cause overstimulation of plant growth. Numerous derivatives are available for agricultural and domestic use [253]. The most commonly used agents include 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2-methyl-4-chlorophenoxypropionic acid. Many preparations contain more than one chlorophenoxy herbicide or other types of herbicides. Despite extensive use of these agents, fatality and significant toxicity are limited. The chlorophenoxy herbicides are notorious because of dioxin contamination in Agent Orange, a 1-to-1 mixture of 2,4-D and 2,4,5-T used extensively in the Vietnam War, so named for the color of the drums used to store it. Agent Orange contained dioxin (2,3,7,9-tetrachlorodibenzodioxin), a contaminant in the synthesis of chlorophenoxy compounds and a potent teratogen in animals [254,255].

Pharmacology

In general, chlorophenoxy herbicides are well absorbed orally. They have small volumes of distribution, large renal excretion, and a low pK_a [253]. 2,4-D has a volume of distribution of 0.1 to 0.3 L per kg and a pK_a of 2.6 to 3.5 [256]. Oral doses of 5 mg per kg in human volunteers produce no ill effects. The peak serum concentration is achieved within 4 to 12 hours [257], 80% of the absorbed dose is eliminated unchanged in the urine, and 13% is eliminated as acid-labile conjugates. The plasma half-life is 18 to 40 hours and varies with urine pH; it may range from 4 to 220 hours [258]. The volume of distribution of 2,4,5-T is 6.1 L per kg. It is exclusively excreted unchanged in the urine, and the plasma half-life is 11 to 23 hours [259].

Various mechanisms of toxicity in humans are postulated. Uncoupling of oxidative phosphorylation has been demonstrated in vitro and may be responsible for a mild heat exhaustion syndrome [260,261]. Chlorophenoxy herbicides can interfere with the TCA cycle and cellular metabolism by forming analogues with acetyl coenzyme A [259,260]. There may be other direct toxic effects on skeletal muscles and peripheral nerves [262].

Clinical Toxicity

GI symptoms are common, and patients frequently experience nausea, vomiting, diarrhea, and abdominal pain [261,263,264]. Ulcerations may occur at the mouth and pharynx, but are uncommon elsewhere in the GI tract [260]. A mild heat exhaustion syndrome consisting of fever, diaphoresis, and hyperventilation can be seen [261,263]. The CNS is particularly affected, and patients may present with confusion, lethargy, convulsions, and coma [263,265]. Prolonged coma (up to 4 days) has been reported with 2,4-D toxicity [266]. Myotonia, rhabdomyolysis, and chronic muscle weakness are also reported [264]. Renal complications may result from rhabdomyolysis and myoglobinuria [267]. Hypocalcemia may occasionally be seen as a result of rhabdomyolysis and hyperphosphatemia [265,268]. Fatality is uncommon, and the cause of death remains unclear [258,260,264,268–270].

Management

Gastric decontamination with lavage should be performed within 1 to 2 hours of ingestion. Skin should be decontaminated with soap and water. Basic supportive therapies include the maintenance of good urine output (1 to 2 mL per kg per hour) with fluid resuscitation and external cooling for hyperthermia. Because of the low pK_a and renal elimination of chlorophenoxy herbicides, urinary alkalinization can significantly enhance renal excretion and decrease the plasma half-life of various chlorophenoxy herbicides [263]. Thus, it should be initiated in patients with significant toxicity by using a sodium bicarbonate infusion to titrate the urinary pH to 7.50 to 8.0. The patient's fluid status should be closely monitored because renal dysfunction may develop from chlorophenoxy herbicide toxicity. Although the utility of extracorporeal elimination of chlorophenoxy herbicides in poisoned patients has not been studied, hemodialysis may be useful for 2,4-D because of its small volume of distribution. Patients with renal insufficiency and significant toxicity would gain the most benefit from hemodialysis.

CHLORATE SALTS

Chlorate salts (sodium chlorate [$NaClO_3$] and potassium chlorate [$KClO_3$]) are nonspecific herbicides. They are also used in the manufacture of explosives, dyestuffs, tanning agents, and matches.

Pharmacology

Chlorates are strong oxidizing agents that result in hemolysis and methemoglobinemia. They have direct toxic effects on the kidneys and indirect nephrotoxicity from hemoglobinuria. Because chlorates are primarily eliminated by the kidneys, nephrotoxicity further enhances their toxicity. The acute lethal dose is 25 to 35 g [271].

Clinical Toxicity

GI symptoms are prominent within hours after an acute exposure and include nausea, vomiting, diarrhea, and abdominal pain [271–273]. Hemolytic anemia and methemoglobinemia result from the oxidizing effects. Both entities may result in a significantly decreased oxygen-carrying capacity and cellular hypoxia [272,274]. Cyanosis may be evident with significant methemoglobinemia. Acute renal failure typically develops within 48 hours after exposure [271,273,275]. Significant hyperkalemia from hemolysis is another potential fatal complication.

Management

Initial supportive care should be directed at the airway, breathing, and maintenance of circulation. Continuous cardiac monitoring should be initiated. Gastric decontamination should be performed within 2 hours after ingestion unless the patient already has significant vomiting. Laboratory studies should

include hemoglobin, serum electrolytes, blood urea nitrogen, creatinine, and methemoglobin concentrations. Electrocardiogram and arterial blood gas should be obtained as clinically indicated. Intravenous or oral sodium thiosulfate (2 to 5 g) has been advocated to inactivate the chlorate ion, but its efficacy has not been clinically proven [276]. Methylene blue should be administered for clinically significant methemoglobinemia, but it may not be effective in the setting of significant hemolysis because intact intracellular enzymes are required for its therapeutic effect [277]. Methylene blue is indicated in patients with a methemoglobin concentration of more than 20% or at a lower value in symptomatic patients with anemia. The initial dose is 1 to 2 mg per kg administered IV over 5 minutes and a response is anticipated within 30 minutes. Subsequent doses of methylene blue can be administered if there is an initial success, but it is withheld if no response is observed. Exchange transfusion may be required for refractory methemoglobinemia or significant hemolysis. Hemodialysis can remove chlorates and is recommended in patients with associated renal dysfunction [271,276].

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CHAPTER 142 ■ PHENCYCLIDINE AND HALLUCINOGEN POISONING

FRANK F. DALY AND LUKE YIP[□]

PHENCYCLIDINE

Phencyclidine (phenyl-cyclohexyl-piperidine, or PCP) is a dissociative anesthetic chemically related to ketamine. PCP is a synthetic compound developed in the 1950s as an anesthetic–analgesic for animals and was used as a general anesthetic in man. However, there was an unacceptably high incidence of postoperative delirium and adverse drug events were not a deterrent for PCP abuse. Tables 142.1 and 142.2 show the slang, or street names, for both PCP and ketamine.

Pharmacology

PCP has acid and alkaloid forms. Both are odorless, nonvolatile, sold as "angel dust," and may be ingested or injected intravenously. PCP acid is a white crystalline substance sold as or incorporated into tablets. It deteriorates when heated and is not suitable for smoking. PCP alkaloid is a grayish–white amorphous powder smoked after incorporation into marijuana (e.g., "super grass," "super weed") or tobacco (e.g., "clickers," "primos") cigarettes. More often, the alkaloid is dissolved in a liquid hydrocarbon and applied to the wrapper of a tobacco cigarette. The ether-like or formaldehyde odor surrounding some patients who have used PCP is the smell of the volatile hydrocarbon used to dissolve PCP alkaloid.

Several analogs of PCP are occasionally used as street drugs (Table 142.3). Their pharmacologic actions are similar to those of PCP and cannot be distinguished clinically. In addition, street PCP samples may be contaminated with 1-piperidinocyclohexane-carbonitrile, a precursor of PCP that is more potent than PCP and capable of generating cyanide [1], although the clinical significance of this is unknown.

PCP has multiple mechanisms of action (Table 142.4), which helps to explain the varied signs and symptoms associated with PCP intoxication. It is well absorbed from the gastrointestinal (GI) and respiratory tracts. PCP is a weak base (pK_a 8.5), has a volume of distribution 6.2 L per kg, and is extensively protein-bound (65%) [2]. PCP concentrates in the brain, lungs, adipose tissue, and liver. The average serum half-life in controlled studies is 17 hours [2]. PCP is metabolized by the liver and excreted predominantly as inactive compounds [2–5]. Small amounts of PCP are excreted in perspiration, saliva, and gastric juice. PCP has been detected in umbilical and infant blood, amniotic fluid, and breast milk [6,7].

Clinical Toxicity

Drinking PCP, injecting intravenous PCP, or swallowing the remnants of a PCP-soaked cigarette has resulted in severe

TABLE 142.1

SLANG TERMS (STREET NAMES) FOR PHENCYCLIDINE

Cyclone	KJ
DOA	Mist
Dust	Rocket fuel
Elephant tranquilizer	Scuffle
Goon	Sernyl
Hog	

□The views expressed do not necessarily represent those of the agency or the United States.

TABLE 142.2

SLANG TERMS (STREET NAMES) FOR KETAMINE

Green	Special K
Jet	Special LA coke
K	Super acid
Mauve	Super C
Purple	

intoxication within 1 hour. Clinical experience with PCP intoxication is derived from case reports [8–15] and small clinical series [16–20]. The hallmarks of PCP intoxication are nystagmus and hypertension. Nystagmus may be horizontal, vertical, or rotary. Patients may have systolic or diastolic hypertension. Hypertension usually resolves within 4 hours, but a significant number of patients may remain hypertensive for more than 24 hours.

Tachycardia is common, but heart rates more than 120 per minute are unusual. Hypothermia (< 36.7°C), hyperthermia (> 38.9°C), respiratory compromise, tachypnea, hypotension, and cardiac arrest are reported, but are uncommon.

Patients may present with delirium or normal sensorium. Lethargy, stupor, and unconsciousness are uncommon presentations. The most common behavioral effects are violent and agitated behavior, which may result in severe penetrating or blunt trauma. Patients may exhibit bizarre behavior such as driving less than 10 mph on the freeway, "playing bumper cars" on the freeway, sleeping on top of cars that are blocking traffic, lying down in a busy street, and wandering or acting wildly in public. Only 20% of PCP users report hallucinations or delusions. The visual hallucinations are typically concrete and realistic (e.g., blue fish). Patients may appear mute or may stare blankly.

The most common neuromuscular finding is rigidity of all extremities. It is often associated with jerky or thrashing movements, tremors, or twitching. Other musculoskeletal disturbances include oculogyric crisis, trismus, facial grimacing, circumoral muscle twitching, lip smacking or chewing movements, torticollis, tongue spasms, opisthotonos, and catalepsy. Patients may exhibit self-limited slow, writhing movements of the extremities or body. Athetosis and muscle stiffness may appear simultaneously. Intermittent athetoid movements may last for more than 10 hours. Rhabdomyolysis may occur, even in calm-appearing patients. Grand mal seizures and status epilepticus are uncommon.

The major autonomic effects are profuse diaphoresis, copious oral or pulmonary secretions, and urinary retention. Bronchospasm has been reported in patients who smoked or sniffed PCP. Pupillary size is usually normal, but miosis or mydriasis may be evident.

Clinically, acute PCP intoxication can be divided into major and minor clinical syndromes [20]. Major syndromes, representing moderate-to-severe PCP intoxication, are delirium, toxic psychosis, catatonic syndrome, and coma. They may include any of the effects previously discussed. Minor syndromes are lethargy or stupor, bizarre behavior, violent behavior, agitation, and euphoria. They represent mild PCP intoxication, and complications are rare.

Delirium is the most common presentation of PCP intoxication. Patients may be found wandering in traffic or appear intoxicated with ethanol. Patients exhibit signs and symptoms such as slurred, bizarre, or repetitive speech; ataxia; disorientation; confusion; poor judgment; inappropriate affect; amnesia of recent events; bizarre behavior; agitation; and violence. The duration of this syndrome often lasts for a few hours and rarely lasts more than 3 days, but has been reported to persist for 1 to 3 weeks.

Patients presenting with toxic psychosis often have a history of chronic PCP use (e.g., smoking) during the week before admission. This psychosis is characterized primarily by hallucinations, delusions, and paranoid ideation. Hallucinations may be auditory or visual, or both, and may involve seeing brilliantly colored objects, but objects are not distorted and there are no kaleidoscopic effects. Patients may be preoccupied with religious thoughts or have religious delusions. It is common for patients to have pressured speech, scream, or make animal sounds. Signs and symptoms persist for a median of 3 days (range, 1 to 30 days).

The catatonic syndrome manifests primarily as a combination of signs: posturing, catalepsy, rigidity, mutism, staring, negativism, nudism, impulsiveness, agitation, violence, and stupor. Stereotypies, mannerisms, grimacing, and verbigeration may also be present. Patients are typically mute, staring blankly, motionless, stiff, standing with extremities or head in bizarre positions, and unresponsive to noxious stimuli. Catatonic syndrome usually does not persist for more than 24 hours (range, 2 to 6 days), and most patients recover within 4 to 6 hours. The majority of patients emerging from catatonic syndrome are agitated or combative for several hours; the other patients emerge with delirium, lethargy, psychosis, bizarre behavior, or normal sensorium.

Patients with delirium and violent or bizarre behavior may subsequently lapse into coma. Coma may also occur abruptly and may last up to 6 days. Patients emerging from coma may exhibit delirium, catatonic syndrome, toxic psychosis, stupor, agitation, violence, bizarre behavior, or normal sensorium. The duration of the emergent phenomenon is variable.

TABLE 142.3

PHENCYCLIDINE ANALOGS USED AS STREET DRUGS

PCE (cyclohexamine)
PCPP (phenylcyclopentylpiperidine)
PHP (phenylcyclohexylpyrrolidine)
TCP (thienylcyclohexylpiperidine)

TABLE 142.4

PHENCYCLIDINE PHARMACOLOGY

Sites	Actions
N-methyl-d-aspartate receptor	Glutamate antagonist
D_2 dopamine receptor	Blocks dopamine reuptake Interferes with dopamine release
Serotonergic receptor	Antagonist
Cholinesterase	Antagonist
Nicotinic receptor	Antagonist
Muscarinic receptor	Anticholinergic effects may include tachycardia, mydriasis and urinary Cholinergic effects may include miosis salivation and diaphoresis Binds to receptors in the heart
Na^+ and K^+ channels	Antagonist
Presynaptic brain neurons	Increase catecholamine release

Data from references [53–63].

Violent, agitated, and euphoric patients typically have a clear sensorium. Patients with euphoria may report a sense of well being or feeling "spaced out," "freaked out," or "tingling all over." Such behavior usually lasts several hours.

Neonatal jitteriness, hypertonicity, and vomiting have been associated with maternal PCP abuse [21]. Chronic PCP intoxication has not been described, and there is no documentation of PCP flashbacks.

Diagnostic Evaluation

PCP intoxication is a clinical diagnosis. It is based on a history of possible PCP exposure associated with clinical findings consistent with PCP intoxication and the exclusion of other neuropsychiatric or behavioral disorders. The drug history should include the type of product, method of use, time of exposure, circumstances surrounding intoxication, and description of any effects witnessed by others or experienced by the patient. Particular attention should be paid to any abnormal behavior that might have resulted in occult trauma (e.g., jumps or falls).

The physical examination should focus on the vital signs, sensorium, behavior, and musculoskeletal, autonomic, and neurologic findings. A thorough examination should be performed to exclude occult trauma. Explosions in clandestine laboratories may lead to smoke or chemical inhalation, thermal or chemical burns, and blunt or penetrating trauma.

Laboratory tests should include complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine, glucose, creatine phosphokinase (CPK), liver function tests, and urine analysis to include myoglobin. Common abnormal test results associated with PCP intoxication include hypoglycemia, elevated white blood cell count, serum CPK, serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase, and uric acid. Chest radiograph, electrocardiogram, arterial blood gas, computed tomography of the head, and lumbar puncture should be obtained as clinically indicated.

Serum or urine PCP levels can confirm the diagnosis of PCP intoxication but neither contributes to the patient management nor correlates with the severity of intoxication [22]. Rapid urine qualitative drug screens that detect PCP should be interpreted with caution. Dextromethorphan use may lead to false-positive PCP results on urine qualitative drug screens [23]. Diphenhydramine may interfere with PCP determination by gas–liquid chromatography [24].

Management

The immediate management is to assess and treat acute threats to the airway, breathing, and circulation. Close monitoring of the patient in a quiet area with limited stimuli may reduce the need for physical restraint or sedation and provide a safe environment for the patient, attending staff, and other patients. Routine gastric decontamination is not recommended.

Patients with major PCP intoxication syndrome or complicated minor PCP intoxication syndrome should be managed in an intensive care unit. These patients should receive supplemental oxygen, secure vascular access, and have their vital signs and cardiac rhythm continuously monitored. A core temperature should be obtained in all patients.

Hemodynamic effects of PCP usually do not require specific treatment. Abnormal vital signs should be managed in the context of the overall clinical status of the patient. Mild sinus tachycardia or hypertension not associated with psychomotor agitation or evidence of end organ damage usually does not require pharmacologic treatment. Treatment of psychomotor agitation using benzodiazepine sedation often results in improvement or resolution of sinus tachycardia and hypertension. Persistent significant hypertension despite resolution of psychomotor agitation, or if there is evidence of end organ damage, should be treated with intravenous nitroprusside or nitroglycerin titrated to effect. The use of β-adrenergic or calcium-channel antagonists to treat drugs of abuse-induced tachycardia or hypertension is not routinely recommended and may have deleterious effects.

Patients with hypotension should receive fluid resuscitation while alternative causes are considered (e.g., occult trauma). Persistent hypotension refractory to fluids necessitates a vasopressor such as norepinephrine or epinephrine. Pulmonary artery catheter hemodynamic monitoring may provide important data to guide pharmacologic intervention. Cardiac dysrhythmias should be managed according to current Advanced Cardiac Life Support guidelines.

Core temperature approaching or exceeding 104°F (40°C) is immediately life threatening and warrants aggressive management. Rapid-sequence induction, intubation, and ventilation may be required. Completely undress the patient, begin continuous monitoring of the patient's core temperature, and initiate active cooling measures. Active cooling should be terminated when the patient's core temperature approaches 101°F (38.3°C). Antipyretics (e.g., acetaminophen, aspirin, non-steroidal anti-inflammatory drugs) are not useful, and there is no good evidence that dantrolene, bromocriptine, or amantadine enhances the cooling process in patients with life-threatening hyperthermia.

The initial management of a patient with altered mental status should include assessment and treatment of all readily reversible causes such as hypoxia, hypoglycemia, opioid toxicity, and thiamine deficiency. Imaging studies of the head should be performed on patients with persistent altered mental status, followed by lumbar puncture as clinically indicated. Antibiotic and antiviral medications should be administered as soon as the diagnosis of meningitis or encephalitis is entertained.

Mild psychomotor agitation usually does not require active intervention, but sedation becomes necessary for patients whose behavior poses a danger to themselves or others. Haloperidol and chlorpromazine have been reported to be safe and effective in the management of patients with PCP intoxication who exhibit violent or bizarre behavior [20,25–27]. Benzodiazepines may be preferred treatment for patients with major or minor PCP syndromes; however, benzodiazepines lack anticholinergic and extrapyramidal side effects, do not lower seizure threshold, and have not been associated with hyperthermia or neuroleptic malignant syndrome. The dose of benzodiazepine should be titrated to achieve moderate sedation to obviate physical restraints. Occasionally, large doses (e.g., > 100 mg of diazepam) may be necessary to achieve safe gentle sedation. The patient's ability to protect the airway should be carefully monitored. Intubation and ventilation are rarely necessary.

Seizures should be treated with incremental doses of intravenous benzodiazepine. Cumulative high-dose benzodiazepine may be required. If seizure activity is not rapidly controlled, intravenous propofol or phenobarbital is indicated. Seizures refractory to sedative hypnotic drugs should be managed with non-depolarizing neuromuscular blockade and general anesthesia, along with continuous electroencephalogram monitoring.

Fluid management should address any electrolyte and acid–base abnormalities. Management of rhabdomyolysis should include treatment of psychomotor agitation and generous intravenous crystalloid fluids to maintain urine output of at least 2 to 3 mL per kg per hour to minimize the risk of acute tubular necrosis. The role of alkalinizing the urine to provide renal protection when rhabdomyolysis is present is controversial. As serum myoglobin levels are not usually rapidly available, serum CPK may be monitored noting that the clinically

important myoglobin serum peak may precede the CPK peak by several hours. Care should be taken to prevent dependent muscle injury.

Although urinary acidification can increase renal PCP excretion [9], the risks associated with urinary acidification outweigh potential benefits [10]. Hemodialysis is not indicated for enhanced drug elimination but may be necessary in patients with acute renal failure.

Patients with persistent suicidal ideation or psychosis should be referred to the psychiatric service.

HALLUCINOGENS

Psychedelic hallucinogens are primarily composed of synthetic indolamines (derivatives of tryptamine), phenethylamines (derivatives of amphetamine, see Chapter 144), and plant products. The psychedelic experience may precipitate homicidal acts [28–30], self-destructive behavior [31], accidental injuries, and acute or chronic psychosis. Physiologic effects vary from mild flushing to life-threatening alterations in vital signs, coma, seizures, and coagulopathy.

Pharmacology

Synthetic hallucinogens are sold as liquid, powder, tablets, capsules, microdots (dried drug residue) on printed paper, liquid-impregnated blotter paper, and as windowpanes (translucent 3 × 3 mm gelatin squares).

The routes of administration are oral, intranasal, sublingual, conjunctival, smoking, or intravenous injection. Blotter paper is chewed and swallowed, whereas microdot paper is usually licked. Windowpanes are usually placed under the tongue or in the conjunctival sac, and may also be swallowed.

The mechanisms of action for psychedelic hallucinogens are presumed to involve various neurotransmitters in the central nervous system. Psychedelic hallucinogen effects on thought and perception appear to primarily involve serotonin (5-hydroxytryptamine) neurotransmission. Serotonin modulates psychological and physiological processes such as affect, mood, personality, sexual activity, appetite, motor function, pain perception, sleep induction, and temperature regulation [32]. Serotonin causes vasoconstriction in all vascular beds except for coronary arteries and skeletal muscles, in which it causes vasodilation.

Tryptamine derivatives have been shown to act at presynaptic type 2 serotonin receptors (i.e., serotonin reuptake sites) [33]. Some of these compounds appear to be partial agonists or agonist–antagonists at these receptors.

Hallucinogens are readily absorbed from the GI tract, metabolized by the liver, and excreted predominately as pharmacologically inactive compounds. The clinical effects produced by different agents are very similar.

Lysergic acid (LSD, or "acid"), the most widely abused tryptamine derivative, was originally synthesized from an ergot alkaloid. The usual street form is a 1 cm^2 piece of blotter paper ("tabs"). At doses of 100 μg, LSD produces perceptual distortions and hallucinations.

Morning glory (*Ipomoea* and *Rivea* genera) seeds contain lysergic acid derivatives that are one tenth as potent as LSD. Users report that to achieve the desired hallucinogenic effect requires ingestion of 200 to 300 macerated seeds.

Psilocybin and psilocin are tryptamine derivatives found in *Psilocybe* and other hallucinogenic fungi ("magic mushrooms"). It is usually sold in the form of dried mushroom, capsules, or paper packets of brown powder. Pure psilocybin is available in capsules of white powder. The effective psilocybin dose is 5 to 15 mg, which is equivalent to ingestion of one to five large mushrooms. However, the clinical effects are dependent on a number of factors, including dose, method of preparation, and individual patient factors [34].

The toads of the genus *Bufo* secrete a mixture of hallucinogenic tryptamine derivatives and cardioactive compounds on their skin [35,36]. Toad licking has been popularized by the belief that hallucinogenic effects may be achieved by licking the skin of live toads.

Dimethyltryptamine (DMT) is an endogenous serotonin metabolite and is also found in the Yakee plant (*Virola calophylla*), which is native to the Amazon basin. Street DMT is available as liquid or yellow-tan powder that is sprinkled on tobacco, marijuana, or parsley and smoked. DMT is broken down in the GI tract; there is minimal systemic absorption after ingestion.

Mescaline, another amphetamine congener, is the psychedelic constituent of peyote (North American dumping cactus, *Lophophora williamsii*) and other cacti. Small segments of the crown of the cactus, known as "buttons" or "moons," may be swallowed whole or chopped into small pieces. Ground peyote may be smoked. The hallucinogenic dose of mescaline is 300 mg, corresponding to 6 to 12 buttons.

Clinical Toxicity

Acute psychedelic effects ("trip" or "tripping") are characterized by changes in sensory perception. They include euphoria or dysphoria; an increase in the intensity of sensory perception; distortions of time, place, and body image; visual hallucinations; synesthesias (i.e., "seeing sounds" and "hearing colors"); illusions; loss of spatial sense; and feelings of unreality. The visual hallucinations are characteristically nebulous, rapidly changing, and unreal (e.g., streaks and blobs of color or kaleidoscopic, multicolored shifting patterns). Visions and mystical experiences have been described [37]. Hallucinogenic drug effects may be variable, even in the same individual on different occasions. The person is usually awake and may appear hyperalert, but is often quiet, calm, withdrawn, depressed, uncommunicative, and oblivious to surroundings or preoccupied with internal stimuli. For some people, the psychedelic experience may be frightening or terrifying, which results in anxiety, agitation, violence, or panic (e.g., a "bad trip" or "bummer"). In general, tryptamine, amphetamine derivatives, and mescaline have clinical effects similar to those of LSD. The most common presentation is acute panic reactions. Patients typically present with anxiety, apprehension, a sense of loss of self-control, and frightening illusions.

The effects of LSD typically begin within 30 to 60 minutes, peak at 2 to 4 hours, and return to baseline within 12 hours. Accidental LSD ingestion by children has resulted in hyperactivity, tachycardia, and hyperventilation [38]; in one case, the reaction was described as "stark terror" [39]. The initial effects of morning glory seeds are listlessness, apathy, and irritability, followed by mild LSD-type effects. Severe psychedelic reactions have been reported [40–42]. Psilocybin effects usually last less than 4 hours but prolonged psychedelic effects have been reported after ingestion of 200 psilocybin mushrooms [43]. The effects of DMT are milder, occur sooner, and have shorter duration than those of LSD [44].

Hallucinogenic mushroom abuse has been associated with facial flushing, salivation, lacrimation, tachycardia, hypertension, mydriasis, nausea, vomiting, diarrhea, and hyperreflexia. Chills and myalgias may also occur [45].

Severe or life-threatening autonomic effects following hallucinogenic intoxication are rare and usually occur only after large doses. Manifestations include stupor or coma, bradycardia or tachycardia, shock or hypertension, severe hyperthermia, seizures, muscle rigidity, and coagulopathy.

No deaths directly attributable to the toxic effects of LSD have been reported. However, massive LSD overdose has resulted in severe autonomic effects such as coma, toxic psychosis, hyperventilation, respiratory arrest, hypertension, hyperthermia, tachycardia, athetosis, dystonic movements, and coagulopathy [46,47]. Serotonin syndrome has been associated with LSD use [48,49].

Intravenous injection of *Psilocybe* mushroom extract has resulted in systemic autonomic effects [45,50].

Persistent LSD effects rarely include prolonged psychotic reactions, depression, exacerbation of preexisting psychiatric illness, and hallucinogen-persisting perception disorder (flashbacks). Hallucinogen-persisting perception disorder is a chronic disorder that occurs after cessation of the acute intoxication and is characterized by recurrence of intrusive images. It can be triggered by stress, illness, and exercise. Flashbacks have been reported after LSD [51], morning glory seeds [41,42], and psilocybin [43] intoxication.

Diagnostic Evaluation

Psychedelic hallucinogen intoxication is a clinical diagnosis. It is based on a history of possible psychedelic hallucinogen exposure associated with clinical findings consistent with psychedelic hallucinogen intoxication. The drug history should include a history of prior drug abuse and psychiatric illness. Often, the name of the drug is not given but the route of intoxication and dosage form are described (e.g., "ate a paper," "chewed a button," "put acid in my eye"). Sometimes the only history is "on a trip."

Physical examination should focus on eliciting signs of autonomic disturbances, synesthesias, illusions, hallucinations, delusions, and abnormal behavior. Laboratory tests should include serum electrolytes, blood urea nitrogen, creatinine, glucose, CPK, and urinalysis. Urine toxicology screen may confirm the diagnosis of psychedelic hallucinogen intoxication and may be useful in patients with unexplained hallucinations. Quantitative hallucinogen drug levels are not clinically useful and do not contribute to patient management. Although laboratory tests are available for LSD and its metabolite [52], it is not part of most standard drug abuse screens. Electrocardiogram, arterial blood gas, imaging studies, and lumbar puncture should be obtained as clinically indicated.

Management

Management of psychedelic tryptamine is the same as for PCP. Patients should be placed in a quiet area with limited stimuli accompanied by a patient advocate. The advocate should provide reality testing and reassure the patient that it is a drug-induced experience and the adverse drug event will resolve within a few hours. This approach may not be practical or effective for severely disturbed or uncommunicative patients, and liberal intravenous benzodiazepine doses should be administered to achieve the desired effect. Depressed or withdrawn patients are unpredictable and should be kept under close observation. GI decontamination is unlikely to benefit a symptomatic patient and is not indicated. Cyproheptadine may be considered in patients exhibiting serotonin syndrome (see Chapters 66 and 124). Patients are expected to completely recover within 24 hours. Persistent signs and symptoms may be due to a psychiatric condition precipitated by the psychedelic drug, and the patient should be referred to the psychiatric service.

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CHAPTER 143 ■ SEDATIVE–HYPNOTIC AGENT POISONING

ANDIS GRAUDINS

Sedative–hypnotics include benzodiazepines (BZDs), barbiturates, non-BZD nonbarbiturate agents (NBNBs), and some muscle relaxants. The barbiturates and "bromides" were the first to become available. In the 1960s, the NBNBs, such as meprobamate (Miltown), were introduced and became popular. NBNBs have been mostly supplanted by the BZDs, which have greater efficacy and a larger therapeutic ratio, and are currently one of the most widely prescribed classes of drugs (Table 143.1). BZDs and their derivatives are used to treat anxiety, depression, panic disorders, insomnia, musculoskeletal disorders, seizures, and alcohol withdrawal, and are used as adjuncts for anesthesia and procedural sedation.

BENZODIAZEPINES

Pharmacology

BZDs exert their therapeutic effect at specific BZD receptor sites in the central nervous system (CNS) [1]. The BZD receptor is located within the γ-aminobutyric acid-A (GABA-A) receptor supramolecular complex (GRSMC). Binding of GABA or GABA plus a BZD causes an allosteric change in the GRSMC. This results in an alteration in chloride-channel permeability, with an increase in chloride flux and hyperpolarization. GABA is an inhibitory neurotransmitter, and its receptors form an inhibitory bidirectional system with connections within many areas of the CNS. Once neurotransmission has been altered, there is a secondary effect on neurotransmitter release from the internuncial neurons. For the most part, activation of a GABA neuron leads to changes in dopamine release, although norepinephrine and acetylcholine may be involved. Serotonin effect is minimal except for neurons in the dorsal raphe [2]. Activation of GRSMC by a BZD potentiates synaptic GABA-mediated inhibition [3,4]. The GRSMCs are located throughout the brain and the spinal cord area. The BZD receptors are categorized as omega 1, omega 2, and omega 3. Each of the omega subtypes tends to cluster in particular areas of the CNS [2,5–7]. The omega-1 subtype predominates in the sensorimotor cortex and is predominantly sedative–hypnotic. The omega-2 subtype is concentrated in the limbic areas of the brain with mainly anxiolytic and anticonvulsant properties [2,3].

BZD absorption from the gastrointestinal (GI) tract depends on the properties and pharmaceutical formulation of each drug. Peak levels occur within 3 hours post-ingestion; intramuscular absorption can be erratic and delayed. Duration of action is dependent on the lipophilicity of each compound; the more

TABLE 143.1

SEDATIVE–HYPNOTIC AGENTS

Benzodiazepines	Nonbenzodiazepine nonbarbiturates
Alprazolam	Alpidem
Bromazepam	Baclofen
Brotizolam	Buspirone
Chlordiazepoxide	Chloral hydrate
Clobazam	Chlormethiazole
Clorazepate	Ethinamate
Diazepam	Ethchlorvynol
Estazolam	Glutethimide
Flunitrazepam	Meprobamate
Flurazepam	Methaqualone
Halazepam	Methyprylon
Lorazepam	Paraldehyde
Midazolam	Zolpidem
Nitrazepam	
Oxazepam	
Quazepam	
Triazolam	
Barbiturates	
Amobarbital	
Aprobarbital	
Butalbital	
Mephobarbital	
Pentobarbital	
Phenobarbital	
Secobarbital	
Thiopental	

lipophilic, the shorter the duration of action. BZDs are highly protein-bound (85% to 99%). Their volume of distribution depends on lipid solubility and varies from 0.26 to 0.58 L per kg for chlordiazepoxide to 0.95 to 2.00 L per kg for diazepam. BZDs are metabolized by hepatic microsomal oxidation (N-dealkylation) and then glucuronidation [8,9]. They can be classified on the basis of elimination half-life (Table 143.2).

Fatality from pure BZD overdose is rare. Toxicity may vary between individual agents. Alprazolam overdose was found to result in more frequent intensive care unit admission, mechanical ventilation, and flumazenil use than other benzodiazepines [10]. A retrospective review of 1,239 overdose cases from one medical examiner's office revealed only two deaths solely related to diazepam overdose [11]. In chronic abusers, rapid clinical recovery after BZD overdose is believed to result from adaptation or tolerance to the depressant effect [12].

Clinical Presentation

Overdose commonly occurs as a part of polydrug ingestions. BZDs alone produce slurred speech, lethargy, ataxia, nystagmus, and coma. Loss of deep tendon reflexes and apnea are unusual except with a massive overdose. There are rare case reports of coma, cardiac arrest, acute respiratory distress syndrome, and pulmonary edema [12–15]. Abrupt cessation of BZDs after long-term use may result in a withdrawal syndrome [16,17] (see Chapter 145).

Diagnostic Evaluation

Recommended laboratory studies include serum electrolytes, blood urea nitrogen, creatinine, and glucose. Because BZDs may be involved in polydrug overdoses, serum acetaminophen levels and a 12-lead electrocardiogram (ECG) results should

TABLE 143.2

DURATION OF ACTION AND ELIMINATION HALF-LIFE ($T^{1}/_{2}$) OF BENZODIAZEPINES

Agent	Duration (h)	Elimination $t^{1}/_{2}$(h)	Peak effect (h)	Active metabolites
Ultra-short–acting	< 10			
Midazolam (Versed)		2–5	0.3–0.8	−
Temazepam (Restoril)		10	2–3	−
Triazolam (Halcion)		1.7–3.0	0.5–1.5	+
Brotizolam		5	1	−
Short-acting	10–24			
Alprazolam (Xanax)		11–14	0.7–1.6	+
Lorazepam (Ativan)		10–20	2	−
Oxazepam (Serax)		3–21	1–2	−
Bromazepam		8–20	1–2	−
Flunitrazepam		20–30	2–8	+
Estazolam		10–24	1	−
Long-acting	> 24	5–30	2–4	+
Chlordiazepoxide (Librium)		36–200	1.0–2.5	+
Clorazepate (Tranxene)		10–50	1–4	−
Clonazepam (Klonopin)		20–50	1–2	+
Diazepam (Valium)		50–100	3–6	+
Flurazepam (Dalmane)		26–200	6	+
Quazepam		11–77	1–3	+
Clobazam		14	1–3	+
Halazepam		Metabolites: 50–100		+
Prazepam (Centrax)		25–41 Metabolites: 40–114	6	+

also be obtained. Creatine phosphokinase (CPK), urine analysis, arterial blood gas, imaging studies, serum salicylate concentrations, and lumbar puncture should be obtained as clinically indicated. Quantitative BZD levels are not useful in the clinical management of overdose cases.

Management

The most important aspect of BZD overdose management is supportive care. Airway management should precede all interventions, and intubation is indicated if the patient cannot adequately maintain spontaneous ventilation or protect the airway. Vascular access should be established. The patient should be placed on continuous pulse oximetry and cardiac monitoring. Activated charcoal (1 g per kg) may be considered in awake patients if the presentation is within 1 hour of ingestion, but there is currently no evidence to suggest that administration changes outcome following simple BZD overdose and may in fact be harmful in patients who subsequently become sedated if the airway is unprotected. Charcoal administration is often not practical as many adult patients, presenting with deliberate self-poisoning, do so more than 2 hours post-ingestion [18]. Additionally, the risks of charcoal administration in a sedated patient with isolated benzodiazepine ingestion must be weighed against the low risk of morbidity and mortality seen with this type of poisoning. There is no evidence to suggest that repeat-dose charcoal enhances BZD elimination [19].

Flumazenil (Romazicon, Anexate) is a BZD antagonist that binds to the GRSMC omega-1 and -2 subtypes, competitively inhibiting BZD binding and thereby reversing BZD sedative and anxiolytic effects [20]. It may also reverse BZD-induced respiratory depression, obviating the need for intubation, but this effect is inconsistent. It does not fully reverse the amnestic effects of BZDs. Patients may appear awake and alert, but subsequent recall (e.g., of instructions) may be poor [21,22].

For most patients with pure benzodiazepine poisoning, supportive care with attention to airway and ventilatory status is all that is required to manage their overdose. It is uncommon for patients to require administration of flumazenil to treat sedation alone. This agent should never be considered in place of airway intervention in compromised patients. Adverse drug events associated with flumazenil use include anxiety, nausea, agitation, and crying. It should be avoided in patients who are suspected to be BZD-tolerant [23]. Flumazenil may precipitate an abrupt withdrawal syndrome with potential for seizures in these patients. This may occur after short-term use of benzodiazepines [24]. Flumazenil should also be avoided in patients with polypharmacy overdoses in whom reversal of BZD effect may unmask the epileptogenic effects of the other drugs (e.g., cyclic antidepressants, isoniazid, and cocaine). Flumazenil is contraindicated in patients with electrocardiographic evidence of cyclic antidepressant toxicity (e.g., prolonged QRS duration), as this finding is associated with a high risk of seizures [25]. Patients with a history of epilepsy are also at increased risk for seizures. Flumazenil has been suggested for both diagnostic purposes in undifferentiated coma and therapeutic purposes. Despite this, its role and indications remain unclear in the management of the BZD-poisoned patient [23]. Flumazenil does not reduce hospital length of stay or need for high-dependency monitoring. If administering flumazenil, the initial dose should be 0.05 to 0.1 mg. This can be repeated at 30-second intervals. In general, if there has not been any response after a total dose of 1 to 2 mg, the diagnosis of benzodiazepine poisoning is unlikely. In the uncommon situation where it may be used to reverse toxicity in deliberate self-poisoning, the aim is to titrate a flumazenil dose such that the patient is moderately drowsy and easily aroused, and *not* to have the patient completely awake, alert, and keen to self-discharge from hospital. Because flumazenil has a short half-life (approximately 50 minutes), it may be administered as an infusion in severe BZD poisoning, in a similar fashion to naloxone in severe opioid poisoning [26]. Seizures that result from flumazenil therapy may require treatment with large doses of BZDs or barbiturates (e.g., thiopental or phenobarbital).

Treatment of BZD withdrawal is similar to that for barbiturates and other nonbarbiturate sedative–hypnotics (see later discussion here and Chapter 145).

BARBITURATES

Barbiturates were the cornerstone of sedative–hypnotic therapy until the 1970s. Since then, the incidence of barbiturate overdose has declined, coincident with their diminishing use [27].

Pharmacology

Barbiturates depress the activity of all excitable tissues. They enhance GABA postexcitatory inhibition at the nerve terminal and appear to have a binding site on the GRSMC, leading to increased chloride flux. The CNS is most sensitive, with skeletal and smooth muscle depression evident at higher doses.

Barbiturates are available in all forms, although most toxicity results from ingestion. Barbiturates are divided into groups based on their duration of action. Ultra-short–acting barbiturates are highly lipid soluble and rapidly partition into the CNS, with subsequent redistribution to all tissues. When parenterally administered, they have rapid onset with less than 1-hour duration of effect; their predominant role is in induction of anesthesia.

Short- and intermediate-acting barbiturates are intermediate in lipid solubility and are used as anxiolytics and sedatives. Long-acting barbiturates have relatively low lipid solubility and are mainly used as anticonvulsants. Systemic toxicity tends to be a function of the drug's elimination half-life (Table 143.3).

Barbiturates are well absorbed from the GI tract; serum levels and symptoms are detectable within 30 minutes, and their peak effect occurs by 4 hours. Barbiturates are variably metabolized by the liver, with most of the highly lipid-soluble group excreted after glucuronidation. The longer-acting barbiturates rely more on urinary excretion for elimination (phenobarbital, 25% to 33%; barbital, 95%; primidone, 15% to 42%; phenylethylmalonamide a metabolite of primidone, 95%) [28]. As they are weak acids, renal elimination can be enhanced by urinary alkalinization. The kinetics of barbiturate elimination are mixed: first order at low concentrations and zero order at high ones [29]. Therapeutic serum drug levels are 10 to 40 µg per mL for phenobarbital and 1 to 5 µg per mL for the short-acting barbiturates. Toxic dosages are in the range of 6 to 10 g for the long-acting barbiturates and 3 to 6 g for the short-acting ones. Most patients demonstrate some degree of sedation with levels of 8 mg per kg. Tolerance rapidly develops, and chronic users may require 5 to 10 times the normal dose for sedation. Depending on the degree of tolerance, drug levels associated with coma range from 80 to 120 µg per mL for phenobarbital and 15 to 50 µg per mL for short-acting agents. Other sedatives (e.g., ethanol) have an additive effect and can result in toxicity at lower doses and blood concentrations [30].

Clinical Manifestations

The most common toxic scenario results from accidental or intentional oral barbiturate ingestion by a seizure patient or family member. Barbiturates may be involved in polypharmacy overdoses, particularly butalbital, a component of several common headache medications (e.g., Fiorinal).

TABLE 143.3

DURATION OF ACTION AND ELIMINATION HALF-LIFE ($t_{1/2}$) OF BARBITURATES

Barbiturate	Duration (h)	Elimination $t_{1/2}$ (h)
Ultra-short–acting	< 1/2	
Thiopental (Pentothal)		6–46
Thiamylal (Surital)		NA
Methohexital (Brevital)		1–2
Short-acting	3	
Hexobarbital (Sombulex)		3–7
Pentobarbital (Nembutal)		15–48
Secobarbital (Seconal)		19–34
Intermediate-acting	3–6	
Amobarbital (Amytal)		8–42
Aprobarbital (Alurate)		14–34
Butabarbital (Butisol)		34–42
Butalbital (Fiorinal, Esgic)		NA
Long-acting	6–12	
Barbital		48
Mephobarbital (Mebaral)		48–52
Phenobarbital (Luminal)		24–144
Primidone (Mysoline)		10–12

NA, not available.
Adapted from Harves SC: Hypnotics and sedatives, in Goodman L, Gilman A (eds): *The Pharmacological Basis of Therapeutics*. 8th ed. New York, Macmillan, 1990, p 357.

Most patients present with some degree of sedation, which is evident within 30 minutes after ingestion of the agent. This may rapidly progress to coma, respiratory collapse, and hypotension. The patient may be mildly hypothermic from loss of autonomic function and decrease in overall muscle activity. The CNS depression is generalized, although there are many reports of focal findings [30,31]. Cardiovascular collapse with severe hypotension is believed to be due to direct myocardial suppression and vascular dilation, an indicator of serious toxicity. Dysrhythmias are rare. The gut becomes atonic, producing delayed absorption or ileus, which may then progress to bowel necrosis. Bullous skin lesions over pressure points occur in 6% of patients within 24 hours of ingestion [32,33]. The lesions are tense clean bullae surrounded by erythema, and the bullae fluid has detectable amounts of barbiturate. The presence of bullae is not pathognomonic for barbiturate poisoning. Bullae formation has also been reported following other sedative–hypnotics, tricyclic antidepressants, methadone, and carbon monoxide poisoning. Crystalluria has been reported [34].

Withdrawal symptoms may occur after 1 to 2 months of chronic use. Symptoms usually present after 2 to 7 days of abstinence or four to five elimination half-lives. Agitation, hyperreflexia, anxiety, and tremor are the most common symptoms, followed by confusion and hallucinations. In early withdrawal, up to 75% of patients experience seizures. Barbiturate withdrawal seizures appear to be more severe than ethanol withdrawal seizures. Transplacental tolerance occurs, with neonatal irritability noted for months after birth [35].

Diagnostic Evaluation

Serum phenobarbital concentration should be determined in situations where phenobarbital or primidone overdose is suspected. However, results of other serum barbiturate concentrations are generally not available in a clinically meaningful time. Recommended laboratory studies include complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine, glucose, and liver function tests. Because barbiturates may be involved in polydrug overdoses, serum acetaminophen concentration, to exclude occult ingestion, and an ECG should also be obtained. CPK, urine analysis, arterial blood gas, imaging studies, and lumbar puncture should be obtained as clinically indicated.

Management

The most important aspect of barbiturate overdose management is supportive care. Early airway management is imperative, as up to 40% of patients may suffer from pulmonary aspiration. Frequent monitoring of all vital signs, including rectal temperature, is indicated. Vascular access should be obtained. The patient should be placed on continuous pulse oximetry and cardiac monitoring. A single dose of activated charcoal (1 g per kg) should be considered in large ingestions with appropriate airway protection.

Multiple-dose activated charcoal (MDAC) and urinary alkalinization can enhance the elimination of phenobarbital and possibly other barbiturates [36–38]. In a human volunteer study, MDAC was superior to urinary alkalinization in enhancing elimination of intravenously administered phenobarbital [39]. MDAC is recommended for all barbiturate overdoses, and urinary alkalinization is recommended for those involving long-acting agents such as phenobarbitone.

Hypotension should initially be treated with intravenous normal saline. Because its etiology is multifactorial, hypotension unresponsive to intravenous crystalloids challenge should be treated with dopamine or norepinephrine. Invasive hemodynamic monitoring and supportive therapy should be considered in severe or refractory cases. Cardiovascular instability unresponsive to conservative measures is also an indication for extracorporeal drug removal. Hemoperfusion (clearance, 100 to 300 mL per minute for phenobarbital) removes more drug than hemodialysis (clearance, 60 to 75 mL per minute), but more modern high-flow hemodialysis has the potential to be as effective as hemoperfusion, especially if combined with multiple-dose oral charcoal [40–42]. On completion of treatment, serum drug concentrations may rebound because of redistribution, and repeat hemodialysis/hemoperfusion may be necessary. Hypothermia requires rewarming. The patient should be monitored for development of aspiration pneumonia, acute respiratory distress syndrome, and electrolyte derangement.

Barbiturates suppress brain electrical activity, and an isoelectric electroencephalogram is not necessarily an indicator of poor prognosis; full recovery has been reported in patients with an isoelectric tracing.

Barbiturate withdrawal should be managed in a controlled environment with adequate resuscitation equipment available because seizures and cardiovascular collapse may occur. Because almost all sedative–hypnotic agents are cross-tolerant, barbiturate withdrawal can be treated with reinstitution of the same drug or another sedative–hypnotic (e.g., BZDs) in equipotent doses (Table 143.4). The goal in therapy is to suppress signs and symptoms of withdrawal. Patients should initially be given sufficient amounts of drug to induce sedation. Using an agent with a long duration of action (e.g., phenobarbital) maintains the serum concentrations, thereby limiting the side effects and cravings associated with falling levels. The dose is decreased by 10% every 3 days. If the equivalent phenobarbital dose is unknown, 120 mg can be administered orally or intravenously every 1 to 2 hours until withdrawal symptoms resolve or drowsiness ensues [17,43].

TABLE 143.4

SEDATIVE–HYPNOTIC EQUIVALENTS

Diazepam, 5 mg, is equivalent to	
Oxazepam	30 mg
Chlordiazepoxide	25 mg
Flurazepam	15 mg
Clorazepate	3.75 mg
Lorazepam	1 mg
Triazolam	0.5 mg
Alprazolam	0.25 mg
Phenobarbital, 30 mg, is equivalent to	
Pentobarbital	100 mg

Adapted from references [43,99].

Tolerance can be ascertained by the pentobarbital suppression test. The patient is given phenobarbital, 200 mg, every 2 hours until sedation occurs. If the initial 200 mg does not cause sedation, tolerance is present. If more than 1,200 mg is required to produce sedation, the patient will most likely experience withdrawal symptoms.

NONBENZODIAZEPINE, NONBARBITURATE SEDATIVE–HYPNOTICS

NBNB sedative–hypnotics include glutethimide (Doriden), ethchlorvynol (Placidyl), meprobamate (Miltown), chloral hydrate (Noctec), and the antispasmodic–muscle relaxants carisoprodol (Soma) and baclofen (Lioresal). Toxic effects and overdoses can be seen from legitimate and illicit use. Newer agents have also been introduced that vary in their toxicity in overdose. These include buspirone, an azaspirodecanedione that binds to 5-hydroxytryptamine receptors; zopiclone, a cyclopyrrolone with sedative–hypnotic activity; and zolpidem and alpidem, which are imidazopyridine sedative–hypnotic and anxiolytic agents, respectively. Many of these medications have a high abuse potential secondary to their ability to induce tolerance and dependence. In addition, a large percentage of those who use and abuse these medications have a history of psychiatric disorders and concurrent ethanol abuse.

Chloral Hydrate

Chloral hydrate was first introduced in 1869 and is still used for sedation in pediatric patients [44]. It is rapidly absorbed from the GI tract, with onset of action within 30 minutes. Chloral hydrate undergoes hepatic biotransformation by alcohol dehydrogenase. The principal metabolite trichloroethanol (TCE) has a longer half-life (4 to 12 hours) than the parent compound. When alcohol dehydrogenase is inhibited by 4-methylpyrazole, increased sedation is seen in 4-methylpyrazole–treated rats after chloral hydrate administration [45]. This suggests that the parent compound is more sedating than TCE and that the previously held belief that acute ethanol ingestion enhances TCE production and sedation may not be the case. However, acute chloral hydrate metabolism inhibition by ethanol may explain the additive effect of ethanol on chloral hydrate sedation ("Mickey Finn") [45]. The metabolism of chloral hydrate to TCE is age-related, with an increasing elimination half-life as the neonate ages to toddler [46]. In neonates, the glucuronidation pathway is still immature and chloral hydrate competes with bilirubin. In addition, renal clearance is limited due to immature kidney function. This can lead to direct hyperbilirubinemia in the neonate [46–48]. Saturation kinetics leading to prolonged elimination has been demonstrated in cases of overdose [49].

There has been a number of reports regarding pediatric chloral hydrate toxicity [49,50]. The lethal dose in adults is 5 to 10 g, but as little as 1.25 g has been fatal. Patients have survived reported doses as high as 36 g [51,52]. Toxicity develops within 3 to 4 hours after ingestion and is manifested by significant GI irritation, ranging from gastritis to perforation [53]. Other findings include CNS depression, pinpoint pupils, hypothermia, hypotension, and respiratory depression. Paradoxic CNS excitation, particularly in children, has been reported coinciding with peak plasma levels (1 to 3 hours) [48]. Myocardial depression results from decreased myocardial contraction and decreased refractory period. Cardiac dysrhythmias such as multifocal premature ventricular contractions, supraventricular dysrhythmias, and ventricular tachycardia have been reported [54].

Tolerance and addiction can develop in chronic abusers. The addicted patient may take very large doses of the drug and can suffer a withdrawal syndrome similar to that from alcohol [55]. Because this drug is hepatotoxic, the abuser may experience unexpected liver failure, leading to acute intoxication and death at doses that were previously tolerated [56].

The treatment of chloral hydrate poisoning is primarily supportive. All patients with a suspected ingestion should have an established intravenous line and continuous pulse oximetry and cardiac monitoring. Activated charcoal (1 g per kg) should be considered in symptomatic patients presenting early post-ingestion with appropriate airway protection. As chloral hydrate is radiopaque, large ingested amounts may be seen on abdominal radiographs.

Cardiac dysrhythmias may not respond to standard antidysrhythmics, such as lidocaine. Beta-blockers (e.g., propranolol 1.0 mg IV) may be of benefit [57]. Ventricular dysrhythmias may be partly due to TCE sensitization of myocardium to endogenous catecholamines similar to other halogenated hydrocarbons. Hypothermia can generally be treated with passive rewarming. Hemoperfusion may be considered in patients with prolonged coma, refractory dysrhythmias, or hypotension [58]. TCE clearance by hemodialysis varies between 120 and 162 mL per minute. In one patient who ingested 38 g, the half-life decreased from 35 to 6 hours after hemodialysis [58].

Ethchlorvynol

Ethchlorvynol is a hypnotic with muscle relaxant and anticonvulsant activities. Clinical effects are apparent within 15 to 30 minutes, and peak levels are seen in 1 to 2 hours. Ethchlorvynol is highly lipid-soluble and is stored in adipose tissue and the brain. It has a unique half-life, being 10 to 25 hours in therapeutic ingestions but up to 100 hours in very large overdoses. Ninety percent of the drug is metabolized by the liver. The patient may present with an altered sensorium ranging from dizziness to facial tingling, giddiness, excitement, dysarthria, ataxia, mydriasis, nystagmus, or areflexia after smaller doses. Severe overdose is characterized by profound and prolonged coma (more than 1 week), hypothermia, respiratory depression, hypotension, and bradycardia [59]. Comatose patients may have an isoelectric electroencephalogram. Seizures may occur after acute ethchlorvynol ingestion. A sometimes clinically useful property of ethchlorvynol is its aromatic and quite pungent odor, described as similar to that of a new car or plastic shower curtain. It may be detected on the patient's breath.

As in other medications of this group, chronic abuse of ethchlorvynol resulted in tolerance and dependence. Sudden

withdrawal can be confused with delirium tremens or an acute psychotic reaction [60].

Treatment is supportive. Hemoperfusion effectively clears the drug [61]. However, lipid redistribution of the drug means that repeated hemoperfusion may be necessary.

Glutethimide

The toxic dose of glutethimide is more than 3.0 g, with a usual fatal dose being 10 to 20 g. Glutethimide is highly lipid-soluble and displays two-compartment kinetics, with rapid intake in the brain followed by systemic distribution. Gastrointestinal glutethimide absorption is erratic, but its onset of action is 20 to 30 minutes [62]. Glutethimide is metabolized in the liver to an active metabolite, 4-hydroxy-2-ethyl-2-phenylglutarimide [62], which has a longer duration of action and is more potent than the parent compound [63]. It also stimulates the hepatic microsomal enzyme system and has considerable anticholinergic activity.

Acute glutethimide overdose is similar to that seen with barbiturates. Profound and prolonged coma is similar to that seen with ethchlorvynol. Glutethimide has been reported to produce thick and tenacious bronchial secretions. The most unique aspect of acute glutethimide intoxication is the fluctuating level of consciousness [63]. The reason for this is unclear, but theories include enterohepatic recirculation of the drug and its metabolites, prolonged absorption of the parent compound from an anticholinergic-induced paralytic ileus, and redistribution from adipose stores. Increased intracranial pressure, seizures, areflexia, and muscular twitching may be evident. Hypotension, hypothermia, persistent acidosis, and cardiac arrest have all been reported [63]. The chronic use of glutethimide leads to tolerance and addiction.

Glutethimide was frequently abused as a combination drug with codeine. Most preparations containing codeine also contained acetaminophen. This combination of glutethimide and Tylenol No. 3 or Tylenol No. 4 was called "loads" or "fours and doors."

The mainstay of treatment for glutethimide poisoning is supportive care. Because there may be significant anticholinergic-induced delay in gastric emptying, late administration of activated charcoal may be effective. Treatment with MDAC may increase glutethimide and 4-hydroxy-2-ethyl-2-phenylglutarimide elimination because of its known enterohepatic circulation. Case reports suggest that charcoal hemoperfusion may hasten recovery from coma, but this has never been examined in a controlled fashion [64].

Meprobamate and Carisoprodol

Meprobamate (e.g., Equanil, Miltown, Bamate, Neuramate) is an unusual member of this class of medications. It has antianxiety and muscle-relaxant effects in addition to sedative properties. Meprobamate is available in regular and sustained-release formulation. Toxicity can be seen in ingestions as small as 2.0 g and fatalities with as little as 12 g [65]. Survival has been documented with doses as high as 40 g.

Meprobamate is rapidly and completely absorbed after an oral dose [65]. Peak effect is seen in 3 hours, with a half-life of 10 hours. Most patients feel an effect for up to 36 hours. The drug is largely metabolized in the liver, induces microsomal enzymes, and its inactive metabolites are excreted in the urine. Very little of the drug is plasma protein-bound.

The clinical picture of meprobamate poisoning is similar to that of the other medications in this class, with predominately CNS and respiratory function impairment [65]. Hypotension is primarily mediated by a fall in systemic vascular resistance dysrhythmias, and palpitations [66]. Persistently elevated serum levels may indicate ongoing drug absorption from bezoar formation. Levels more than 20.5 mg per dL have been associated with CNS depression and coma. A withdrawal-abstinence syndrome beginning 1 to 2 days after cessation can occur even after chronic daily ingestions of as little as 1.6 g. Treatment of meprobamate poisoning is similar to that for the other medications in this class. MDAC may be of value after large ingestions because of potential for gastric concretion formation [67]. Hemoperfusion hastens drug clearance and should be considered in patients with cardiovascular compromise or failure to improve despite aggressive supportive treatment [68].

Carisoprodol (Soma, Rela) is a congener of meprobamate used as a muscle relaxant. Carisoprodol is metabolized in the liver and excreted in the urine, with an elimination half-life of 4 to 6 hours. Some of the ingested dose is metabolized to meprobamate by CYP2C19 [69]. The predominant side effect of the drug is drowsiness. Rarely seen idiosyncratic reactions include asthenia, transient quadriplegia, dizziness, ataxia, diplopia, agitation, confusion, and disorientation. Its toxicity and treatment are otherwise similar to those of meprobamate [70].

Baclofen

Although usually not considered a sedative or hypnotic drug, baclofen (Lioresal) toxicity may mimic that of sedative–hypnotics, and treatment is similar. Baclofen is a potent GABA-B agonist. Its primary use is as an antispasmodic agent, decreasing flexor tone and spasm in certain neurologic diseases. Therapeutic doses of baclofen are 15 to 60 mg per day. Baclofen is cleared by the kidney, with only a small portion hepatically transformed. Baclofen is well absorbed from the GI tract. Elimination is by first-order elimination kinetics, with a half-life of 2 to 6 hours after therapeutic dosing. Intrathecal baclofen is being used increasingly to treat intractable spasticity in children and in patients with spinal cord injury. Complications such as baclofen overdose and withdrawal syndrome may be related to pump malfunction, refilling mistakes, and programming mistakes related to adjustment of pump flow rate [71,72].

Hypotension and hypertension have been reported with baclofen toxicity [73]. Coma, seizures, severe myoclonus, apnea, and hypothermia may be evident [74]. Cardiac effects include prolonged PR and QTc intervals, junctional escape beats, premature atrial contractions with block, supraventricular tachycardia, and bradycardia [73]. Myoclonus and hyporeflexia have also been reported as well as seizure activity documented on EEG monitoring [71].

Management following baclofen either by the oral or intrathecal route intoxication is primarily supportive. Mechanical ventilatory support is often required after overdose [73]. Baclofen, in a large overdose, is more slowly absorbed from the GI tract than after a single therapeutic dose, suggesting that the administration of activated charcoal may be of benefit. Symptomatic bradycardia responds to atropine [75]. Hypotension commonly responds to intravenous fluids. Ventilatory assistance may be required for prolonged periods, averaging 3 to 7 days [76]. Patients have been observed to be persistently symptomatic up to 60 hours post-ingestion even when serum baclofen levels are undetectable [77]. Benzodiazepines should be used to control seizure activity or myoclonus.

Baclofen withdrawal syndrome (Chapter 145) may result after sudden cessation of oral baclofen therapy or in patients being treated with intrathecal baclofen where there may be pump failure and reduced baclofen delivery. Withdrawal may present with mental status changes, delirium,

hallucinations, hypertension, hyperthermia, myoclonus, hyperreflexia, seizure activity, and may mimic signs of serotonin syndrome or neuroleptic malignant syndrome in some cases [71,78]. A close evaluation of the baclofen pump is essential in these cases to identify any potential dosing errors or malfunction with the pump system. Treatment includes supportive care and reinstitution of baclofen therapy as soon as practicable, but may also require the acute use of high-dose parenteral benzodiazepines to attenuate symptoms and signs of neuromuscular hyperexcitability and seizure activity [78,79].

Buspirone

Buspirone is a serotonergic and dopaminergic active drug with minimal sedative–hypnotic effects during therapeutic dosing. It also has central acetylcholine and norepinephrine effects. Its mechanism of action is not fully understood, but it appears to interact with exogenous and endogenous BZD, binding at the GRSMC as well as 5-hydroxytryptamine receptors. At low doses, it is predominately anxiolytic, although it may take several weeks to reach this effect. At high doses, it can cause sedation similar to that seen with BZDs (20 mg per day), but the sedation is much less than that seen with an equivalent dose of the BZD. It is well absorbed orally, and peak serum levels occur within 1 to 2 hours. It is hepatically metabolized, with an elimination half-life of 2 to 3 hours.

Adverse drug events reported during therapeutic dosing include weakness, GI distress, dysphoria, headache, and dizziness. It may cause a withdrawal syndrome after prolonged use but does not cross-react with BZDs in treating BZD withdrawal. Flumazenil does not reverse buspirone effect.

Buspirone has been an uncommon drug in overdose settings. Serotonin syndrome has rarely been reported when buspirone has been added to therapy in patients prescribed selective serotonin reuptake inhibitor medications such as fluoxetine, fluvoxamine, and sertraline [80–82]. Supportive care is the mainstay of therapy after an overdose.

Zopiclone

Zopiclone is a non-BZD agent with sedative–hypnotic, anxiolytic, and muscle-relaxant properties but is predominately marketed as a hypnotic agent. It appears to bind to the GRSMC, possibly with its own binding site. It has been found to displace diazepam and flunitrazepam from their BZD binding sites. It is well absorbed orally, with peak plasma concentration within 30 to 90 minutes. It undergoes first-order kinetics of distribution and is extensively metabolized. Elimination occurs by the kidneys and lungs. Absorption is significantly affected by gastric emptying. Adverse drug events include a bitter taste in the mouth, and there is carryover sedation into the next day. There may be a morning-after amnesic effect. After chronic dosing, physical dependency and withdrawal have been reported. It may also potentiate the sedative effects of ethanol.

Isolated zopiclone poisoning commonly follows a similar benign course to that of benzodiazepine poisoning [83]. Patients with concurrent ethanol or other sedative ingestion may develop significantly greater sedation. Observation and supportive care is the mainstay of therapy. Isolated reports have noted mild to moderate and delayed onset (14 to 16 hours postingestion) methemoglobinemia (10 to 23%) following zopiclone overdose [84]. This may be related to production of large amounts of an N-oxide metabolite of the parent drug [84]. Zopiclone poisoning has been reported to respond to flumazenil [85].

Zolpidem and Alpidem

Zolpidem and alpidem are imidazopyridine agents used as hypnotic and anxiolytic agents, respectively. Both bind to the GRSMC, zolpidem at the omega-1 and alpidem at the omega-1/omega-3 receptor binding sites. Both agents are rapidly absorbed orally, highly protein-bound, and hepatically metabolized. Zolpidem has an elimination half-life of 2.5 to 5.0 hours and alpidem of 8 to 20 hours. Adverse drug events associated with zolpidem use include anxiety, dizziness, drowsiness, fatigue, headache, diplopia, diarrhea, tremor, and hangover effect with anterograde amnesia. Alpidem use has been associated with adverse drug events such as sedation, headache, dizziness, insomnia, nausea, and vomiting. Alpidem has been reported to increase serum hepatic transaminase levels. Tolerance, dependency, and subsequent withdrawal are possible. Coingestion with other sedative agents, including alcohol, will result in increased sedation.

The most common findings seen after zolpidem overdose include sedation and respiratory depression. Cardiovascular or ECG changes do not occur in isolated zolpidem toxicity. Death has been reported with the combination of overdose with zolpidem and other CNS depressants, although no deaths have been reported with zolpidem overdose alone [86]. Treatment of overdose is predominately supportive. Flumazenil has been used to reverse the effects of zolpidem in overdose [87].

γ-Hydroxybutyrate

γ-Hydroxybutyrate (GHB) was originally used as an anesthetic induction agent and subsequently found to be a naturally occurring GABA metabolite in the CNS. It does not interact with GABA-A receptors, and as a result, its effects are not antagonized by flumazenil [88]. The mechanism of action of GHB may result from its interaction with specific GHB receptors, GABA-B receptors, and by elevation of CNS dopamine and endorphin levels [88]. GHB can be administered orally or parenterally with clinical effects occurring within 30 minutes of ingestion. Metabolism is by succinate semialdehyde to succinate, which enters the Krebs cycle and is eventually metabolized to carbon dioxide and water. GHB is also excreted (2% to 5%) unchanged in urine [89].

γ-Hydroxybutyrate can be obtained illicitly by mail order in powder form and reconstituted to a liquid. GHB is commonly produced in illicit backyard laboratories in the United States. Recipes for its production can be found on the Internet. Production begins with γ-butyrolactone, which is treated with an alkali such as sodium hydroxide to open the lactone ring to produce GHB when heated. If the pH of the solution is not back-titrated with acid, it may result in a highly alkaline solution. Esophageal burns and subsequent stricture formation has been reported after ingestion of an alkali GHB solution [90]. GHB is abused for its hypnotic and euphoric effects recreationally and may also have been used as a date-rape drug. Many states in the United States have categorized GHB as a Schedule-1 controlled substance.

"Pine needle oil" contains 1,4-butanediol and has been reported to induce a similar toxicity to GHB. Alcohol and aldehyde dehydrogenase catalyze the conversion of 1,4-butanediol to GHB, resulting in a clinical syndrome similar to GHB toxicity. This reaction can be inhibited by ethanol, 4-methylpyrazole, and disulfiram [91]. Butanediol and γ-butyrolactone are freely available for legal purchase over the Internet in many countries. As both are metabolized to GHB when ingested and result in similar toxicity, they are often purchased instead of GHB to avoid legal prosecution [92].

Symptoms of GHB toxicity occur rapidly after ingestion and may be potentiated by alcohol and other sedative agents, including opioids. Death has resulted from mixed intoxication with opioids [93]. Drowsiness, euphoria, hallucinations, delirium, nausea, vomiting, hypothermia, seizures, and coma can be seen. Recovery from pure GHB poisoning is typically rapid with return of consciousness within a few hours of ingestion [94]. Mass exposures have been reported in the popular press, usually in the setting of a dance rave, party, or nightclub [95]. Chronic use can lead to tolerance and physical dependence. A withdrawal syndrome comprising anxiety, agitation, paranoia, and visual and auditory hallucinations has been reported [96].

Management of GHB intoxication is supportive. Airway protection and ventilatory support are the mainstay of therapy. Prolonged sedation may indicate coingestion of other sedative agents. Flumazenil (GABA-A receptor antagonist) and physostigmine (short-acting acetylcholinesterase) do *not* reverse sedation [97,98] and may result in unwanted toxic effects of the respective antidotal agent. Because GHB is usually ingested as a liquid formulation and has a rapid onset of action, activated charcoal is unlikely to be beneficial.

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CHAPTER 144 ■ AMPHETAMINES

MICHAEL C. BEUHLER

INTRODUCTION

The term "amphetamine" includes a wide range of amine compounds with sympathetic-like effects. The simplest member of this group is amphetamine, but there are hundreds of molecules with related chemical structures that have similar clinical effects. This chapter will focus on the more important and commonly used licit and illicit members of this group.

Amphetamine and methamphetamine are the most well-known members of this class. **Amph**etamine or **a**lpha-**m**ethyl **phe**nylethylamine was first synthesized over 120 years ago, and it was widely used by many (including the U.S. military) as the stimulant Benzedrine, beginning in the 1930s. Restricting to

prescription decreased use slightly, but it has been continued to be used for both licit (Attention deficit hyperactivity disorder [ADHD], narcolepsy, and weight loss) and illicit reasons. Currently, Adderall® (a mixture of *l* and *d* amphetamine) and Vyvanse® (Lisdexamfetamine; metabolized to *d*-amphetamine) are two commonly used medicinal amphetamine preparations.

Methamphetamine (or N-methyl amphetamine) is undergoing a surge in United States and worldwide popularity. One reason for its popularity over amphetamine is its longer duration of action. Another reason is that the Drug Enforcement Agency has taken actions to limit the availability of precursor compounds for the synthesis of amphetamine, including the unrelated removal of phenylpropanolamine from the OTC market. Finally, synthesis can be conducted by individuals without specialized training using materials that are not difficult to obtain, resulting in a relatively pure product. Currently, Desoxyn® is a methamphetamine containing prescription preparation used for ADHD and obesity.

There are several other medicinal compounds that have clinical effects similar to amphetamines, with a select few discussed here. Ritalin® (methylphenidate) is commonly used in children for ADHD and is occasionally abused. Phenylpropanolamine (Dexatrim®) was used more extensively in the past as a decongestant and weight loss agent; in 2005 the FDA removed it from OTC sales due to concerns about increased stroke risk and it is no longer available as an Rx [1]. Ephedrine has been used extensively in the past in herbal weight loss/energy preparations as well as a decongestant in cough/cold preparations; but in 2004, the FDA prohibited the sale of dietary supplements containing ephedra (ephedrine and pseudoephedrine) over safety concerns. Additionally, in 2006, requirements regulating the sale of ephedrine were enacted in an attempt to limit its diversion for methamphetamine synthesis. Phentermine is an amphetamine derivative that is used for appetite suppression. Selegiline is an amphetamine derivative with selective monoamine oxidase inhibitor (MAOI)-B effects that is metabolized to l-methamphetamine. Propylhexedrine (Benzedrex® nasal inhaler), although not a true amphetamine, has sympathomimetic and vasoconstrictor properties and is occasionally abused.

Some amphetamine analogs with aromatic ring substitutions have direct affinity for serotonin receptors as well as increased inhibition of serotonin uptake, thereby exerting both sympathomimetic and serotonergic effects manifested by hallucinatory properties. One of the more popular compounds in this group is 3,4-methylenedioxy-methamphetamine (MDMA or Ecstasy). Other similar ring-substituted amphetamine compounds include 3,4-methylenedioxy amphetamine (MDA), 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA or Eve), 2,5-dimethoxy-4-bromo-phenethylamine (2-CB; not strictly an amphetamine), para-methoxy amphetamine (PMA), 2,5-dimethoxy-4-methyl-amphetamine (DOM), and 2,5 dimethoxy-4-bromo-amphetamine (DOB; also the similar chlorine and iodine derivatives DOC and DOI exist). The 2,5 dimethoxy halogenated amphetamine derivatives (DOB, DOC, DOI) are common substitutions for LSD found on blotter paper in the United States [2].

Recent increases in clandestine methamphetamine production facilities ("meth labs") have resulted in concern for environmental contamination and bystander toxicity from laboratory chemicals. The vast majority of illicit amphetamine laboratories currently produce methamphetamine by reductive dehydroxylation of ephedrine or pseudoephedrine. Methamphetamine laboratories are often discovered after a chemical mishap or explosion and are a health risk due to the chemicals used, which include respiratory irritants and caustics [3]. Methcathinone is a potent, occasionally used amphetamine-like substance produced from the *oxidation* of ephedrine in amateur labs, instead of the usual *reduction* to methamphetamine; toxicity is similar except that cases of Parkinson-like neurotoxicity from manganese in the impure product have been reported.

There are two methods most commonly being utilized for methamphetamine synthesis. The one resulting in the cleanest product probably the more dangerous one is the Birch or "Nazi" method, which utilizes lithium metal as the reducing agent dissolved in anhydrous ammonia. The other method is the hydriodic acid method, which usually utilizes red phosphorus and iodine, as the availability of hydriodic acid is restricted.

Depending upon the illicit amphetamine purchased, there is a chance that it will contain one or more contaminants, or possibly be substituted by another sympathomimetic. Street purchased methamphetamine tends to be of better purity than cocaine, while MDMA is very commonly substituted or combined with other psychoactive substances. The exact "contaminants" or other chemicals present in street purchased amphetamines are highly variable based on drug, year, and location. Previously reported substitutions include acetaminophen, anesthetics (benzocaine, lidocaine, procaine), cocaine, caffeine, ephedrine, ketamine, lead (rare), talc, phencyclidine, piperazine compounds (benzylpiperazine and others), phenylpropanolamine, pseudoephedrine, strychnine, and quinine [4]. Depending on the quantity of the adulterant, it may contribute to the effect or toxicity of the sympathomimetic drugs.

Occasionally, an individual will ingest an amphetamine while it is wrapped in plastic or other non-permeable material. Body *packers* or "mules," are people who transport large quantities of specially prepared drug packets in their gastrointestinal (GI) tract. Each packet usually contains drugs in sufficient quantity and purity to cause life-threatening toxicity if rupture occurs. Body *stuffers* are people who quickly swallow ("stuff") drug-containing packets in an attempt to get rid of evidence and avoid arrest by the police. These packets are usually poorly prepared and are at increased risk of leakage and rupture, but often contain far less drug than a packet from a body packer. Rarely, individuals will ingest a plastic bag containing a drug with holes or a corner of the bag cut off in an attempt to produce a sustained release effect [5].

PHARMACOLOGY

Amphetamine and methamphetamine are similar in their pharmacokinetic properties and have similar physiological effects in humans [6]. They do not have significant direct effects at adrenergic or dopamine receptors; rather their effects are mediated by an increase in the concentration of synaptic dopamine and to a lesser extent, serotonin and norepinephrine. This increase occurs by several mechanisms. Amphetamine and methamphetamine enter the presynaptic cytoplasm by passive diffusion and uptake by biogenic amine uptake transporters. Amphetamine moves into the synaptic vesicles by diffusion and by the vesicular monoamine transporters (VMATs), subsequently causing release of stored dopamine and norepinephrine, most likely by collapsing the proton gradient as well as an effect on VMAT. This increases the cytosolic levels of these biogenic amines, which then results in increased synaptic levels due to increased reverse transport activity by the amine transporters, especially the dopamine transporter. Part of the mechanism of action of amphetamines' raising synaptic levels is also due to competitive inhibition of biogenic amines reuptake from the synapse into the presynaptic terminal. Finally, some amphetamines have MAOI activity, which inhibits the breakdown of dopamine, serotonin, and norepinephrine, with some (PMA for example) having significant MAOI activity [7,8].

The mechanism of action of MDMA toxicity includes a direct effect at some serotonin receptors, as well as some of the

indirect effects described above mediated by a release of serotonin. Additionally, human and animal studies have shown that MDMA produces a dose-related depletion of serotonin and serotonin transporter activity, and produces serotonergic neuronal degeneration [9]. Methamphetamine causes dopamine and serotonergic neuronal toxicity as well as a decrease in dopamine, VMAT, and serotonin transporter activity in the brain, at least in part by free radical injury [10,11].

Peak plasma concentrations of methamphetamine are reported within 4 hours for an insufflated dose, within 2 to 3 hours for a smoked dose and nearly immediate for an IV dose [12,13]; however levels do not correlate with the degree of clinical toxicity [14]. Methamphetamine and amphetamine have an *l* and *d* isomer; the *d* form is more potent in causing pleasurable CNS stimulation and persistent cardiovascular activation than the *l* form [15]. Most abused methamphetamine is the *d* isomer, having been synthesized from ephedrine or pseudoephedrine. However, the *d* form of methamphetamine has a shorter half-life (10 to 11 hours) than the *l* form (13 to 15 hours) [15,13]. The α-carbon on the amphetamine molecule protects it against MAO degradation. The majority of methamphetamine is either eliminated unchanged, N-demethylated to amphetamine (active) or hydroxylated to p-hydroxymethamphetamine (active) with contribution from cytochrome 2D6 [16,17]; amphetamine undergoes a similar metabolism, except that it is deaminated to an inactive metabolite as well as hydroxylated to p-hydroxyamphetamine (active). Excretion of both is increased in acidic urine, but this fact has no clinical utility as the risks of urinary acidification outweigh any potential benefits. Urine usually remains positive for 24 hours or longer in high dose chronic abusers [18]. The serotonergic amphetamine and amphetamine-like compounds (MDMA, PMA, 2-CB) are not metabolized to amphetamine or methamphetamine.

CLINICAL PRESENTATION

Methamphetamine toxicity has been reported following ingestion, inhalation (smoking), insufflation (intranasal), rectal, subcutaneous, intramuscular, and intravenous exposure [19]. The onset and duration of methamphetamine toxicity depends on factors such as dose, route of exposure, individual tolerance, pattern of use, ambient temperature, and crowding/stimulation level. Most people develop signs and symptoms within a few minutes of parenteral drug use, whereas signs and symptoms may be delayed for hours after ingestion with body packers and body stuffers. In most patients, the majority of sympathomimetic effects are expected to resolve within 24 to 36 hours post exposure [19]. Life-threatening toxicity is more common in drug abusers and in people who overdose with suicide intent, and it can also occur in body packers and body stuffers.

Methamphetamine toxicity usually results in a group of signs and symptoms known as the "sympathomimetic toxidrome," including hypertension, tachycardia, tachypnea, hyperthermia, diaphoresis, mydriasis, hyperactive bowel sounds, agitation, anxiety, and toxic psychosis. This pattern of symptoms is seen for other members of the amphetamine group as well as other sympathomimetics like cocaine and caffeine; but this pattern of symptoms can be variable depending on the sympathomimetic agent involved. For example, phenylpropanolamine has peripheral alpha vasoconstrictive effects that can result in a reflex bradycardia.

Airway and breathing abnormalities are uncommon with ingestion. Transient cough, pleuritic chest pain, and shortness of breath are common after insufflation or smoking. People present in illicit drug laboratory fires and explosions may have thermal injury to their oropharyngeal or upper airway. Insufflation or smoking methamphetamine may result in bronchospasm, pneumothorax, pneumomediastinum, pneumonitis, and noncardiogenic pulmonary edema. Noncardiogenic pulmonary edema and acute respiratory distress syndrome may be associated with multisystem organ failure. Tachypnea is common secondary to agitation or metabolic acidosis. Hypoventilation is rare but may occur secondary to intracranial pathology or the end stage of multisystem organ failure.

Many of the adverse cardiovascular effects result from increases in peripheral catecholamines, which result in a mismatch of oxygen consumption and delivery; there may be a direct cardiotoxic effect of methamphetamine as well. Palpitations and chest pain are common complaints. Acute myocardial infarction due to vasospasm, plaque rupture, and/or thrombosis can occur [20]. Life-threatening atrial or ventricular dysrhythmias, sudden death, and aortic dissection have been reported, with potential synergy if cocaine is also present [21,20]. Coronary artery disease and cardiomyopathy have been reported with chronic amphetamine abuse [14,22,23]. Peripheral vascular ischemia can result from oral sympathomimetic abuse but is uncommon unless an inadvertent intra-arterial injection occurs. Hypotension is unusual but may be secondary to dehydration, myocardial depression, intestinal ischemia, or sepsis.

There are several important findings that may be apparent on the Head-Eyes-Ears-Nose-Throat exam. Mydriasis is common and various forms of nystagmus have been reported. Patients who abuse and binge on sympathomimetic agents are often dehydrated and have dry mucous membranes. Nasal mucosal abnormalities, including nasal septal perforations, are well reported in patients who chronically insufflate cocaine and are possible with insufflation of other sympathomimetics. An increase in dental pathology has been noted in users of methamphetamines, manifested by a distinctive pattern of caries on the buccal smooth surfaces of the posterior teeth and the interproximal surfaces of the anterior teeth. The teeth may be loose, rotting, or crumbling, and are usually beyond salvage. The pathology of these changes is uncertain, but is believed to be due to a combination of decrease in salivation (xerostomia) along with increased ingestion of sugar- and acid-containing sodas, poor hygiene, poor nutrition, localized vasospasm, and bruxism, a side effect especially seen with MDMA. [24,25,26].

Central nervous system effects are the reason for abuse as well as often the reason for seeking care. Methamphetamine produces a euphoric and anorexic effect, with smoked and injected administration producing a greater "rush." The most common presenting symptoms include agitation and altered mental status; other symptoms include headache, hyperactivity, agitation, toxic psychosis, loss of consciousness, focal neurologic deficits, and seizures [27,19]. Hyperthermia may be more common and worse in patients with uncontrolled psychomotor agitation, especially when patients are physically but not chemically restrained. Altered mental status may be secondary to hypoglycemia or an acute intracranial process. Headache may be secondary to intracranial or subarachnoid hemorrhage [21,14,28,29]. Focal neurological deficit may be secondary to cerebral ischemia or infarction, vasospasm, or direct injection trauma. On arteriography, multiple occlusions or "beading" has been observed of the arteries; this is thought to represent some combination of local vasospasm or vasculitis [30,1,28]. Seizures may occur in association with and independent of intracranial hemorrhage or cerebral infarction. Prolonged methamphetamine (and probably MDMA) use may lead to cognitive decline represented by attention and memory changes [11].

Some abusers develop stereotyped, compulsive behavior such as cleaning or buttoning shirts; in some cases it has been observed that addicts compulsively take apart appliances, usually without reassembly. Psychosis from amphetamines is not uncommon and can present as paranoid delusions and

perceptual disturbances; these may persist long after the drug has been stopped and can result in homicidal or self-destructive behavior [31,32,19]. After binge use, patients may develop a withdrawal pattern of symptoms consisting of generalized fatigue, dysphoria, decreased level of consciousness, and profound lethargy.

One occasionally sees choreiform, ballistic, bruxism, torticollis, or athetoid involuntary movements with amphetamine and methamphetamine abuse [33]. These movements can be fast or slow and they can involve the facial, extremity, or trunk muscles. Ataxia may result if the trunk or limb movements are severe enough. These movements usually begin after prolonged abuse of amphetamine or methamphetamine and may become worse or reoccur with additional drug abuse. Usually, the symptoms resolve over several hours to a week following abstinence. However, they may only diminish in magnitude and persist for months or even rarely, years. The movements may be diminished with voluntary motor activity or during sleep. The mechanism for these movements is not well understood, and may involve a disruption of the normal dopamine neurotransmitter system [34].

Abdominal findings may include increased bowel sounds, bowel obstruction from body packing, and abdominal pain due to intestinal ischemia or bowel perforation [35,36]. Psychomotor agitation and seizures can result in rhabdomyolysis [37]. Hyperthermia and multisystem organ failure may result in coagulopathy and disseminated intravascular coagulation (DIC). Hepatic injury progressing to fatal fulminant liver failure can occur from MDMA without any preceding hyperthermia. Dehydration, increased anion gap metabolic acidosis associated with increased lactate, and hypokalemia are common in patients with significant sympathomimetic toxicity. Urinary retention has been reported from amphetamine toxicity. Acute tubular necrosis may occur secondary to hyperthermia, hypovolemia, hypotension, and rhabdomyolysis.

Diaphoresis with either warm or cool skin is common. Scarring and hyperpigmentation ("track marks") in areas above veins suggest chronic intravenous drug use. Skin popping, or subcutaneous injection of the drug can result in scabs, circular scars, and lesions in a variety of areas. Additional excoriations and rashes can result from skin picking and scratching. Abscesses and infection are not uncommon.

Medical complications from drug abuse include endocarditis, hepatitis, human immunodeficiency virus infection, cellulitis, septic emboli, abscesses, tetanus, and wound botulism. Methamphetamine abuse is associated with an increased risk of HIV infection both because of increase in risk taking behavior (IVDA, unprotected intercourse, untreated STDs) and probable enhancement of HIV infectivity [38].

Most of the time, the toxicity observed in the methamphetamine using patient is due to the drug and not from any adulterants. Adulterants are not usually present in large enough amounts, and methamphetamine is relatively pure and sufficiently toxic in its own right. However, some important exceptions should be noted. The addition of benzocaine has caused methemoglobinemia [39]. Intra-arterial injection of a drug may cause injury, possibly potentiated by any talc present. Talc pulmonary emboli have been reported as well, which probably contribute to pulmonary hypertension. Lastly, substitution is more of a problem with the ring-modified amphetamines (MDMA); the real substance present in the street purchased product is likely to be contaminated with or entirely be a piperazine (BZP and others), caffeine, methamphetamine, or some other substituted amphetamine such as PMA.

In addition to having some sympathomimetic qualities, nearly all of the ring-substituted amphetamines (MDMA, DOM) also have hallucinogenic properties likely due to their direct and indirect effect at serotonin receptors. The route of abuse for methylenedioxymethamphetamine (MDMA) is usually ingestion. Methylenedioxyamphetamine (MDA) is an analog of MDMA and has similar effects as MDMA. Serious autonomic reactions include many of the sympathomimetic symptoms discussed above as well as seizures, rigidity, dysrhythmias, and profound hyperthermia with grave consequences (rhabdomyolysis, renal failure, DIC) [40]. Given the increased serotonin levels produced, at least part of this toxicity should be characterized as serotonin toxicity/syndrome.

Some of the ring-substituted amphetamines have specific toxicities. There are several reports of hepatoxicity resulting in hepatomegaly, jaundice, and death caused by MDMA that did not stem from hyperthermia or shock liver; this probably resulted from an immunological component [41,40]. Hyperthermia is more common with the ring-substituted amphetamines, likely from contribution from serotonin toxicity and possibly from mitochondrial uncoupling [42]. Hyponatremia resulting in altered mental status, coma, seizures, cerebral edema, and death is also sometimes seen following MDMA use. This probably results from some combination of inappropriate antidiuretic hormone secretion (SIADH) and from excessive water drinking. SIADH may possibly be more commonly observed in young women from MDMA use, as there seem to be an inappropriately large number of cases in this group. The observed clinical toxicity from PMA or "death" includes hyperthermia, hypoglycemia, hyperkalemia, and prolonged QRS; the effects are similar to MDMA but may be more severe because its dose response curve is steep regarding elevating brain serotonin levels, PMA exposures are often unintentional, and it has significant MAOI activity [43,7,44]. Bromodimethoxyamphetamine (DOB) is highly potent, enough so that a dose (2 to 5 mg) can be found on a small piece of paper possibly being sold as LSD. Large doses of DOB have been reported to result in significant vasospasm that has resulted in seizures and deaths [45].

DIAGNOSTIC EVALUATION

Patients with amphetamine toxicity (sympathomimetic toxicity) should have frequent vital sign determinations including core or rectal temperature measurement, intravenous access, and continuous cardiac monitoring. Those with abnormal vital signs or mental status should have an electrocardiogram, complete blood cell count, electrolyte, blood urea nitrogen, creatinine, glucose, and arterial blood gas determinations. Patients with chest pain, dysrhythmias, or persistent pulse or blood pressure abnormalities should be evaluated for acute coronary or vascular syndromes. Patients with prolonged immobilization, uncontrolled psychomotor agitation, or hyperthermia should have serial CPKs to evaluate for rhabdomyolysis. Those that either have or have had significant hyperthermia or shock should also have liver injury and function tests (lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and coagulation profile) to evaluate for multisystem organ failure and DIC.

Several imaging studies may be warranted for an amphetamine toxic patient, depending on their clinical presentation. Those with respiratory symptoms or chest pain should have a chest radiograph and possibly a chest CT if there is concern for aortic dissection. Patients with headache or seizures should be evaluated for intracranial hemorrhage with computed tomography of the brain. Those with continued suspicion for subarachnoid hemorrhage with a negative CT scan should also have a lumbar puncture [28]. Plain and oral contrast abdominal radiographs may be helpful in detecting drug-containing packets in the GI tract of body packers, but their sensitivity is quite low for stuffers. Experience with abdominal CT and abdominal ultrasound for detection of stuffer packets is limited. A negative imaging study cannot be used to rule out drug packets in the GI tract.

The results of toxicology screening for most drugs of abuse rarely contribute to or alter patient management. However, in the case of sympathomimetic toxicity, the urine drug screen is reasonably sensitive to the recent use of methamphetamine/amphetamine as well as cocaine and can assist in differentiating these syndromes that can be important in management. If toxicology drug screening is essential, health care providers should contact their clinical laboratory to determine included substances as well as causes of false–positive and false–negative results. For example, the ability for immunologically based drug screens to detect MDMA (or similar ring-substituted amphetamines) is highly variable, but there are specific immunologically-based MDMA drug screens available.

A positive drug screen can confirm the presence of amphetamine or similar structured drug, whereas a negative drug screen is non-diagnostic. For amphetamines, the screen is typically reasonably sensitive for use within the last few days, but has terrible specificity. A sampling of some common substances that may cause a positive amphetamine screen are bupropion, chloroquine, clobenzorex, ephedrine, methylphenidate, phenelzine, phentermine, phenylpropanolamine, pseudoephedrine, selegiline, tranylcypromine, trazodone, and Vicks® inhaler [46,47,48]. One should remember that if the result of a toxicology screen is to be used for forensic purposes, the chain of custody should be maintained, and results will need to be confirmed using a more rigorous analytical method such as gas chromatography/mass spectrometry.

Toxicologic and nontoxicologic conditions that may have a similar presentation or that present concomitantly (Table 144.1) should be evaluated for and excluded. A serum lactate level may be helpful in patients with increased anion gap metabolic acidosis of unclear cause. An elevated lactate level would be expected in patients with compromised tissue perfusion (e.g., occurring with shock and intestinal or limb ischemia), in those with hypermetabolic states in which metabolic demands exceed available substrates, or in those with cellular dysfunction in whom normal substrates cannot be used. Other causes of increased anion gap metabolic acidosis (e.g., ethylene glycol, methanol, iron, salicylate) should be investigated when the lactate level is normal or near normal. The possibility of concomitant poisoning with by-products or impurities related to the illicit synthesis of methamphetamine (e.g., phenethylamine derivatives, caffeine, ephedrine, mercury, strychnine, or lead) would be rare, but should also be considered.

TABLE 144.1

DIFFERENTIAL DIAGNOSIS OF AMPHETAMINE TOXICITY

Toxicologic
β-Agonists toxicity (clenbuterol and others)
Black widow envenomation
Cocaine
Dextromethorphan
Methylxanthine toxicity (caffeine, theophylline)
Monamine oxidase inhibitor toxicity
Neuroleptic malignant syndrome
Piperazine compounds (benzylpiperazine and others)
Phencyclidine toxicity (PCP)
Bark scorpion envenomation (found mostly in AZ)
Salicylates
Serotonin toxicity
Strychnine
Withdrawal from sedative–hypnotics, including baclofen, barbiturates, benzodiazepines, clonidine, chloral hydrate, ethanol, γ-hydroxybutyrate, γ-butyrolactone, meprobamate, as well as from β-antagonists such as propofol
Nontoxicologic
Endocarditis
Encephalitis and meningitis
Heat stroke
Intracranial bleed or mass lesion
Pheochromocytoma
Sepsis
Thyrotoxicosis

MANAGEMENT

Patients who present with life-threatening effects from amphetamine toxicity or those that are at increased risk for developing them (such as a packer) should be managed in an intensive care unit (Table 144.2). The overall approach to these patients is aggressive supportive care with supplemental oxygen, sedation, fluid administration, and close monitoring while addressing the specific myriad complications that can occur.

The hemodynamic effects of amphetamines are primarily caused by release of catecholamines and not by a direct effect at receptors. Mild sinus tachycardia and hypertension not associated with psychomotor agitation or evidence of end organ damage usually do not require pharmacologic treatment. Treatment of psychomotor agitation utilizing appropriate benzodiazepine doses will often result in improvement or resolution of tachycardia and hypertension. If benzodiazepines do not provide adequate improvement, rate-related cardiac ischemia may be treated with a beta-blocker, preferably a short-acting and easily titratable agent such as esmolol, or a calcium-channel blocker, being cautious to exclude cocaine toxicity if a beta-blocker is being used. Patients with life-threatening dysrhythmias who are hemodynamically unstable should be cardioverted or defibrillated. Persistent hypertension, especially if there is evidence of end organ damage or hyperthermia, should be treated with benzodiazepines as well as phentolamine, nitroprusside, or nitroglycerin with careful dose titration.

Patients presenting with chest pain should be evaluated for acute coronary syndromes and managed accordingly [23]. Thrombolytic therapy or procedural coronary intervention may be indicated as per current guidelines. In these circumstances, cardiology consultation is recommended, especially since coronary vasospasm is a possibility. Other important potential causes of chest pain such as pneumothorax, pneumomediastinum, infection, septic emboli, and aortic dissection should be ruled out.

Hypotension should be treated with fluids, and patients assessed for comorbid potential life-threatening conditions such as dysrhythmias, acute coronary syndromes, pneumothorax, aortic dissection, hyperkalemia, GI hemorrhage, and sepsis. Persistent symptomatic hypotension that is refractory to

TABLE 144.2

INDICATIONS FOR ADMITTING PATIENTS TO AN INTENSIVE CARE UNIT

Acute coronary syndromes	Multisystem organ failure
Aortic dissection	Peripheral ischemia
Body packer or body stuffer	Persistent psychomotor agitation
Cerebral ischemia or infarction	Pneumothorax
Dysrhythmias	Rhabdomyolysis
Hyperthermia	Seizure
Intracranial bleed	
Myocardial infarction	

fluids necessitates treatment with a direct acting vasopressor such as norepinephrine, epinephrine, or phenylephrine. At times, the choice and dose of vasopressor should be guided by pulmonary artery catheter hemodynamic monitoring or bedside ultrasound.

Management of bronchospasm should include nebulized β_2 agonists (such as albuterol) and anticholinergic agents (such as ipratropium bromide). Noncardiogenic pulmonary edema and acute respiratory distress syndrome should be managed according to current guidelines. The benefit of corticosteroids in patients with sympathomimetic-induced bronchospasm, pneumonitis, and noncardiogenic pulmonary edema has not been well studied, but may be considered in patients with severe or persistent symptoms. Occasionally, pneumomediastinum and pneumothorax following smoking methamphetamine is observed. Patients with pneumothorax may require tube thoracostomy depending on the size of the pneumothorax. For a pneumomediastinum, the work up usually involves an oral contrast imaging study to rule out esophageal perforation, but surprisingly these commonly have a completely benign course.

The initial management of a patient with an altered mental status includes assessing and treating all readily reversible causes such as hypoxia, hypoglycemia, electrolyte abnormalities (especially hyponatremia), opioid toxicity, and thiamine deficiency. Imaging studies of the head should be performed on patients with persistent altered mental status, potentially followed by lumbar puncture if indicated. Mild agitation or anxiety may be treated with oral benzodiazepines. Psychomotor agitation that poses a danger to the patient or others requires more aggressive sedation. Incremental doses of intravenous benzodiazepine should be used to achieve the desired effect, noting that significant doses of benzodiazepines may be required. The role of antipsychotics for controlling agitation should be as an adjunctive therapy and not the primary means of control, but does appear to be safe and efficacious in adult and pediatric populations [19,49,50]. One should recognize the other clinical precautions that accompany the use of this pharmaceutical drug class (EKG changes, NMS, etc.). If agitation is severe, more aggressive measures such as sedation and paralysis may be required to protect the patient and the staff. Restraints should only be used during the relatively short time of gaining control of the agitation using pharmaceutical methods, as the restrained agitated patient is at risk for several adverse outcomes, including sudden death.

Patients presenting with seizures should be treated with incremental doses of intravenous benzodiazepines. If seizures are not rapidly controlled, intravenous propofol or phenobarbital is indicated usually along with intubation to secure the airway. The role for phenytoin is limited in the patient with toxicological causes of seizures and usually should be avoided. Seizures refractory to sedative–hypnotic drugs should be managed with non-depolarizing neuromuscular blockade and general anesthesia along with continuous electroencephalogram monitoring. The work up of seizures should include a CT scan to evaluate for potential physical causes. Patients with intracranial hemorrhage or cerebral infarction should have neurosurgery or neurology consultation as appropriate. As the etiology of the "beading" seen on angiography is uncertain, the role of calcium channel blockers (e.g., nimodipine) and/or steroids for such patients is equally uncertain.

Patients with peripheral vascular ischemia should be managed in conjunction with a vascular service. Intra-arterial administration of α-adrenergic receptor antagonists such as phentolamine may relieve localized arterial vasospasm; if multiple areas of vasospasm are observed, there may be a role for intravenous nitroprusside. This adverse effect may be observed more typically with some of the substituted hallucinogenic amphetamines such as DOB [45]. Accidental intra-arterial injection during intravenous abuse may lead to significant tissue destruction through emboli (e.g., talc and the other cutting agents), thrombosis, and vasoconstriction. There is no consensus on managing these patients although adequate fluid resuscitation, acetylsalicylate, and heparin appear to be reasonable; other interventions that have been used for intra-arterial injection accidents with heroin include intra-arterial phentolamine, thrombolytics, and dexamethasone.

Core temperature approaching or more than 104°F (40°C) should be aggressively managed, as the risk for multisystem organ failure exponentially rises with the temperature. One should undress the patient, initiate active cooling measures, and continuously monitor the patient's core temperature. Active cooling techniques include spraying the patient with cool water, draping with cold water soaked sheets along with large fans for evaporation, ice packs in the axilla and groin, or a cooling blanket possibly used *under* the patient while utilizing evaporative cooling from above. Active cooling should be terminated when the patient's core temperature approaches 101°F (38.3°C). Benzodiazepines are useful in decreasing motor agitation contributing to the hyperthermia. Paralysis and intubation would be a last resort to treating persistent rigidity associated hyperthermia. Antipyretics (e.g., acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs) are not useful, and there is no evidence that dantrolene, bromocriptine, or amantadine enhance the cooling process in these patients with life-threatening hyperthermia.

Fluid management should address any electrolyte and acid–base abnormalities. Management of rhabdomyolysis should include generous intravenous crystalloid fluids to maintain urine output of at least 2 to 3 mL per kg per hour to minimize the risk of acute tubular necrosis. The role of alkalinizing the urine to provide renal protection when rhabdomyolysis is present is controversial, but may be performed if desired. As serum myoglobin levels are not usually rapidly available, serum CPK may be monitored instead. Although no longer recommended for amphetamine toxicity, urinary acidification would increase the urinary excretion of amphetamine but the risks outweigh any potential benefits.

The serotonergic amphetamines MDMA and like compounds can cause significant serotonin toxicity when combined with other pharmaceuticals that have serotonin effects such as SSRIs, MAOIs, and cocaine. Differentiating the degree of concomitant serotonin toxicity can be difficult, but the physical examination findings of myoclonus and hyperreflexia with the lower extremity reflexes more pronounced than the upper extremity reflexes would be strongly suggestive of serotonin toxicity. Treatment is benzodiazepines and supportive care, although cyproheptadine may be of some benefit; an adult dose for serotonin toxicity is 8 mg orally every few hours to a maximum of 32 mg/day. The hyponatremia arising from SIADH should be treated with water restriction and may require hypertonic 3% normal saline. These fluid requirements should be balanced with other fluid issues such as the possible presence of rhabdomyolysis.

The involuntary abnormal choreiform and athetoid movements following abuse may be the reason for presentation and can be a source of great anxiety for the patient. When the symptom onset is rapid and not present for a long period of time, antipsychotics such as haloperidol have theoretical benefit and may be efficacious [33]. When the involuntary movements have lasted for a long time, antipsychotics may be less effective. Sedatives have been observed to increase the movements in some patients. There has been some success in alleviating symptoms using centrally acting antimuscarinic drugs (e.g., benztropine) [34].

There is no consensus on management of asymptomatic body stuffers. Sometimes individuals claim to have ingested drug packets in an attempt to avoid going to jail, a technique which often works in the short term. The count of the number

of packets or the amount of drugs in the packet is usually unreliable. Even when bags or packets are ingested, they are rarely seen on imaging studies. An abdominal CT scan is more reliable than plain abdominal imaging, but false negatives do occur. GI decontamination using activated charcoal (AC) at a dose of 1 to 2 gram per kg should be considered for these patients. Multiple doses of AC have no proven benefit and may be harmful in potentially causing obstruction. The risks of forced AC administration usually outweigh any potential benefit when a patient will not voluntarily drink the AC. However, this risk/benefit ratio should be reassessed should a patient clinically deteriorate to the point of requiring intubation. Occasionally, whole bowel irrigation is also employed for these patients (see below). Given the lack of endpoint (i.e., passed packets) in most of these patients, they will require a period of sufficient observation. The safest approach to these patients would be admission for a minimum of 24 hours of close hemodynamic observation, with additional observation time should any unexplained increase in pulse or blood pressure occur. Note this observation period may not be sufficient for all patients; cases of toxicity have resulted from more than 36 hours from ingestion of a sealed baggie [5].

Asymptomatic body packers should also be conservatively managed. One proposed guideline involves the oral administration of a water-soluble contrast solution followed by serial abdominal radiographs (see Chapter 140, Table 140.5). Whole bowel irrigation (WBI) with isotonic polyethylene glycol electrolyte solution has also been advocated for GI decontamination based on case reports. Some clinicians advocate administering polyethylene glycol solution, 1 L per hour, to adults until there is no longer significant concern for retained packets in the GI tract. This is usually signaled by a clear rectal effluent, no radiographic evidence of drug packets in the GI tract, a negative rectal examination for any packets, and an accurate accounting of the number of ingested packets. It does appear that the packet count for body packers is sometimes more reliable than for body stuffers, but still may not be correct. Administration of multiple doses of cathartics is not considered whole-bowel irrigation and may result in severe fluid and electrolyte abnormalities [51,52,53,54].

Body packers and body stuffers who develop sympathomimetic toxicity should be suspected of having leakage or rupture of the drug packets in their GI tract [55]. In the case of a body packer, this is an absolute indication for emergent surgical intervention due to the massive amount of drug present. Surgical intervention is also indicated for patients with intestinal obstruction, ischemia, or perforation and may be indicated when packets fail to progress through the GI tract after conservative management. Endoscopic retrieval of packets retained in the stomach is rarely performed due to risk of rupture, but if implemented, it should be by an experienced endoscopist.

The proper management of patients exposed to methamphetamine laboratories varies depending on the exposure scenario and the type of laboratory. Many times, the only treatment required is adequate burn care as many of these patients present with thermal burns from a laboratory fire. The most dangerous components to a methamphetamine laboratory (besides the occasional armed psychotic inhabitant) are the possible gases: anhydrous ammonia, hydrochloric acid (HCl), and phosphine. Generally, the HCl and phosphine levels are only present in high enough levels to cause injury during the process of the "cook" [56,57]. All can cause significant pulmonary edema with the injury from phosphine potentially being delayed by several hours and anhydrous ammonia causing significant ocular and dermal injury as well. Methamphetamine laboratories also use caustics and solvents that on contact with skin or eyes can cause significant injury [3]. Variations in the synthesis methods, exposure duration, and preexisting conditions as well as chapter space make it difficult to give further exacting treatment recommendations. It should be noted that despite the subjective complaints, a minor transient exposure to a methamphetamine laboratory is unlikely to cause significant injury, and that unless gross contamination is present, a gentle cleaning with soap and water is adequate for nearly all exposures [58].

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CHAPTER 145 ■ WITHDRAWAL SYNDROMES

PAUL M. WAX AND JENNIFER SMITH

As many as 25% of hospitalized adult patients at a university hospital may have a history of ethanol dependence and abuse [1]. Anticipation and recognition of early signs of sedative–hypnotic withdrawal in the sedative–hypnotic abuser allows timely treatment and prevents development of serious withdrawal manifestations, such as seizures, hyperthermia, and delirium. The management of withdrawal syndromes from γ-hydroxybutyrate (GHB) and baclofen may be particularly challenging. Recognition and treatment of the less life-threatening signs and symptoms of opioid withdrawal avoid unnecessary investigation of the frequently severe gastrointestinal symptoms and make the patient more comfortable and able to cooperate. Because ethanol and other sedative–hypnotic withdrawal may have life-threatening manifestations, patients with signs of significant withdrawal should be admitted to the intensive care unit (ICU) for stabilization and monitoring. In addition, drug-dependent patients admitted to the ICU for management of other serious medical or surgical problems may subsequently enter withdrawal in this substance-free environment [2].

Clinical withdrawal implies the presence of physical tolerance and dependency. Factors contributing to the development of dependency include dose of the drug, duration of effect, frequency of administration, and duration of abuse. Shorter-acting drugs require more frequent administration to produce dependency and are associated with more acute and severe withdrawal symptoms than longer-acting drugs. *Tolerance* is defined as a decreased physiologic response elicited by a given dose of the drug. A patient who chronically ingests large amounts of ethanol may not be sedated by a dose that would render a nondrinker comatose. A heroin abuser who has been drug-free during a year's imprisonment may suffer fatal respiratory depression from a dose of heroin that previously would have provided only mild sedation. This physiologic tolerance to drug effect that occurs with chronic use may arise from changes in drug metabolism, such as increased activity of hepatic microsomal enzyme systems and changes in drug effect at the cellular level [3]. Cross-tolerance occurs when the chronic ingestion of one substance decreases the response to a

second substance. Cross-dependency allows one drug to be substituted for another to prevent withdrawal symptoms. Ethanol, the barbiturates, and nonbarbiturate sedative–hypnotic agents are cross-tolerant and cross-dependent with one another but not with other sedating drugs such as opioids, neuroleptics, or antihistamines. These factors have important therapeutic implications.

ETHANOL WITHDRAWAL

Pathophysiology

Ethanol produces its toxic effects (relaxation, euphoria, disinhibition, slurred speech, ataxia, sedation, stupor, coma, and respiratory depression; see Chapter 119) through modulation of a variety of neuroreceptors and ion channels [4]. It acts, in part, by interacting with the γ-aminobutyric acid ($GABA_A$) receptor complex, potentiating inhibitory GABAergic receptor function by inducing chloride flux through the chloride channels of the receptor complex [5]. Ethanol also inhibits excitatory *N*-methyl-d-aspartate (NMDA) glutamate receptor function, contributing to impaired cognition and blackouts associated with chronic ethanol use [6]. Inhibition of NMDA receptor function changes intracellular calcium levels and, as a result, affects cell-signaling cascades, including phosphorylation [7]. Other neurotransmitter systems affected by ethanol include dopamine and serotonin [8]. Ethanol has been found to affect 5-hydroxytryptamine receptor function by increasing the potency with which agonists bind this receptor [4]. Ethanol consumption may also result in an increase in endogenous opiates, contributing to its euphoric effect [9]. In addition, ethanol may exert its effect by altering the lipid matrix of cell membranes [10]. Although it was not recognized until the 1950s that delirium was a manifestation of ethanol withdrawal rather than toxicity, it is now clear that the hallmarks of ethanol and other sedative–hypnotic intoxication are distinctly different from the manifestations of withdrawal from these agents [11,12].

Ethanol withdrawal produces a hyperadrenergic state characterized by intense sympathetic nervous system activation. This may be due in part to compensatory central nervous system (CNS) mechanisms that counteract the depressant effects of ethanol intoxication. During withdrawal, these compensatory mechanisms are unopposed, resulting in increased neural stimulation [13]. In support of this theory, elevated levels of plasma and urinary catecholamines have been associated with tachycardia, elevated blood pressure, and tremors observed in withdrawing patients [14]. A decrease in the inhibitory activity of presynaptic α_2-receptors has been demonstrated and may explain, in part, the increase in norepinephrine levels [15]. In addition, an increase in β-adrenergic receptors during withdrawal has been demonstrated [16]. One study showed an increase in plasma levels of the dopamine metabolite homovanillic acid in patients presenting with delirium tremens [17].

Compensatory changes in number and function of inhibitory $GABA_A$ receptors and excitatory NMDA glutamate receptors during chronic ethanol use may contribute to the CNS stimulation brought on by the cessation of ethanol. The abrupt withdrawal of the GABA-potentiating effects of ethanol leads to a disinhibition of neural pathways in the CNS [18]. During withdrawal, ethanol's enhancing effect on chloride flux is lost, resulting in a decrease in GABAergic functioning. Tachycardia, diaphoresis, tremors, anxiety, and seizures have been associated with this reduction in GABA-induced chloride flux [19]. Upregulation in NMDA glutamate receptors and changes in their receptor subunit composition increases calcium flux through these receptors [20]. This likely contributes to the excitotoxic neuronal cell death associated with ethanol withdrawal [21]. Repeated episodes of withdrawal increase the propensity for ethanol withdrawal seizures through altered $GABA_A$ and NMDA receptor function [22,23]. Because NMDA receptors mediate dopaminergic transmission, the increased NMDA receptor function that occurs during withdrawal may also lead to decreased dopaminergic and serotonergic transmission, contributing to alcohol craving [7].

Ethanol withdrawal occurs when a dependent patient suddenly stops drinking or drinks at a slower rate than previously. In either case, a significant drop in the serum ethanol level occurs. In chronic alcoholics, signs of withdrawal are commonly present even when their serum ethanol concentrations are higher than 100 mg per dL [24]. Patients admitted to the ICU with ethanol withdrawal often have a significant underlying disease that has led to an inability to maintain an ethanol intake adequate to prevent withdrawal. Alcoholic gastritis, hepatitis, pancreatitis, and pneumonia commonly precipitate decreased ethanol use and withdrawal. These patients typically present to the hospital after 24 to 48 hours of abdominal pain or fever and may be tremulous or have had a withdrawal seizure. Another type of ICU patient prone to withdrawal is one who has continued to imbibe ethanol nearly to the moment of arrival at the hospital. Intoxicated patients are prone to experience traumatic events and arrive in the operating room, recovery room, or ICU still intoxicated. A history of ethanol abuse or previous withdrawal may not be available in the postoperative or intubated patient when initial signs of withdrawal occur. Failure to recognize ethanol withdrawal in the seriously ill or injured patient may lead to prolonged complications [13].

Clinical Manifestations

Ethanol withdrawal results in a variety of signs and symptoms that vary in severity and duration. In their landmark article, Victor and Adams [12] described withdrawal as a tremulous–hallucinating–epileptic–delirious state. Although this description is often used to divide ethanol withdrawal syndrome into four stages, it is important to remember that the various manifestations of ethanol withdrawal form a progressive continuum of severity. A patient in ethanol withdrawal may exhibit one or more of these manifestations. The sequence of clinical events may be inconsistent. The severity of the withdrawal is often dose-dependent, with more severe reactions associated with heavier and longer periods of drinking [24]. It has been suggested that repeated withdrawal episodes produce a kindling effect, such that each subsequent withdrawal elicits increasingly more severe reactions [15,23,24].

Tremulousness and seizures are the most common clinical manifestations of ethanol withdrawal. They tend to occur early and are generally considered mild-to-moderate ethanol withdrawal symptoms. Delirium tremens is a late manifestation of ethanol withdrawal and constitutes the most serious clinical presentation. Although dramatic and life threatening, delirium tremens is but one aspect of ethanol withdrawal and affects 5% of withdrawal patients [25].

Mild ethanol withdrawal is usually characterized by a period of acute tremulousness (the "shakes"). It begins 6 to 8 hours after a reduction in ethanol intake [24,26]. Patients usually complain of tremulousness, nausea, vomiting, anorexia, anxiety, and insomnia. Physical examination reveals evidence of mild CNS and autonomic hyperactivity, which includes tachycardia, mild hypertension, hyperreflexia, irritability, and a resting tremor. Occasionally, significant tremor may not be appreciated despite the patient's complaint of feeling "shaky inside." Despite the fact that patients in delirium tremens have evidence of significant disorientation, this milder form of withdrawal is characterized by a clear sensorium,

although the patient may have a minor disorientation to time. Symptoms of mild ethanol withdrawal usually peak between 24 and 36 hours, and 75% to 80% of these patients recover uneventfully in a few days. Approximately 20% to 25% of patients presenting with mild ethanol withdrawal progress to serious withdrawal manifestations, which include seizures, hallucinations, or delirium tremens. However, it is impossible to reliably predict which patients will deteriorate [24].

Seizures that occur in alcoholics may or may not be due to ethanol withdrawal. Although ethanol withdrawal accounts for many of these seizures, other common causes include preexisting idiopathic and post-traumatic epilepsy [11,12]. Other complications of ethanol abuse not necessarily associated with withdrawal, such as hypoglycemia, hypomagnesemia, and hyponatremia, may also precipitate seizure activity [27]. Ethanol intoxication itself is not thought to be proconvulsant [28]. Alcoholic patients with a history of epilepsy appear to have a greater incidence of seizures than those without a preexisting seizure disorder. Failure to comply with anticonvulsant regimens may, in part, account for this. Brief abstinence (even overnight) may also lower the seizure threshold sufficiently to provoke seizures in susceptible patients. Because management strategies differ depending on whether the patient has a history of previous seizure disorder unrelated to ethanol withdrawal, differentiating between them becomes important [29].

Early studies showed that as many as 25% to 33% of patients in ethanol withdrawal demonstrate seizure activity [11,12]. Most ethanol withdrawal seizures ("rum fits") occur between 7 and 48 hours after cessation or relative abstinence from drinking [30]. Mild-to-moderate signs of withdrawal may precede the seizures, or the seizure may herald the onset of ethanol withdrawal. They are short, generalized, tonic–clonic seizures, 40% of which are limited to a single isolated event. Often a short burst of two to six seizures with normal sensorium between seizures occurs over a few hours. Patients with ethanol withdrawal seizures usually have normal baseline electroencephalograms, in contrast to those with underlying seizure disorders. Status epilepticus or recurrent seizure activity lasting longer than 6 hours is distinctly uncommon in ethanol withdrawal and suggests another diagnosis [31].

Ethanol-related seizures may foreshadow the development of delirium tremens. In one series of patients with ethanol withdrawal seizures, delirium tremens developed in 33% [32]. In some patients, postictal confusion blended imperceptibly into delirium tremens. Approximately 40% of patients in whom delirium tremens subsequently developed exhibited an initial clearing followed by the onset of delirium tremens 12 hours to 5 days later.

Disordered perceptions characterized by hallucinations and nightmares were noted in 25% of tremulous patients in early withdrawal by Victor and Adams [12]. The hallucinations were predominantly visual in nature, auditory only in 20% of cases, and rarely tactile or olfactory. Commonly described visual phenomena in this setting may include the graphic depiction of bugs crawling on the walls or bed [32].

A subset of hallucinating patients does not demonstrate tremulousness or other signs of sympathetic hyperactivity. Known as *acute alcoholic hallucinosis*, this uncommon clinical presentation (occurring in 2% of the patients of Victor and Adams) is a distinct manifestation of ethanol withdrawal that usually begins within 8 to 48 hours of cessation of drinking [12]. It is characterized by disabling auditory hallucinations, often of a persecutory nature. These patients display no evidence of formal thought disorder, have no personal or family history of schizophrenia, and are usually oriented to person and place. In most cases, symptoms last for 1 to 6 days, although they may persist for months and come to resemble chronic paranoid schizophrenia. These symptoms usually respond to therapy with cross-tolerant agents such as benzodiazepines [33].

Delirium tremens is characterized by a significant alteration of sensorium associated with dramatic autonomic and CNS hyperactivity. Only 5% of patients who exhibit any of the previously discussed manifestations of ethanol withdrawal progress to delirium tremens. Delirium tremens appears to be more common in patients with a history of significant withdrawal and a long history of ethanol use. Patients in whom delirium tremens develops may not have demonstrated earlier signs of withdrawal. Other patients who have had ethanol withdrawal seizures or hallucinations may deceptively improve before the onset of delirium tremens, which is rarely seen before 48 to 72 hours after cessation or reduction in drinking and may be delayed for as long as 5 to 14 days [12,26]. These patients are truly delirious, exhibiting disorientation, global confusion, hallucinations, and delusions. Speech is unintelligible. Psychomotor disturbances, such as picking at bedclothes, significant restlessness, and agitation, are common and often require the use of physical restraints. Autonomic disturbances, such as tachycardia, hypertension, tachypnea, hyperpyrexia, diaphoresis, and mydriasis, are present. Cardiac dysrhythmias may also occur [34]. Seizures rarely occur during delirium tremens [26]. Concomitant illness, trauma, seizures, or therapeutic drugs may mask or modify the typical presentation.

Mortality for delirium tremens varies with the presence of underlying disease. Higher mortality is associated with superimposed pneumonia, meningitis, pancreatitis, gastrointestinal bleeding, and major trauma. In the untreated patient without serious coexisting medical disease, mortality usually is a consequence of severe dehydration or hyperthermia, or both, precipitating cardiovascular collapse [35]. Before adequate therapeutic agents were available, a mortality rate of 24% to 35% was cited in the literature [36]. This had decreased to 5% to 10% with the use of barbiturates and paraldehyde [37]. The use of benzodiazepines and intensive supportive care and earlier recognition of withdrawal should further reduce mortality in the absence of significant underlying disease [18].

Diagnostic Evaluation

The differential diagnosis of ethanol withdrawal includes other causes of a hyperadrenergic state. Most importantly, ethanol-related hypoglycemia needs to be differentiated from withdrawal. Clinically, these two conditions may appear remarkably similar, although only hypoglycemia rapidly improves after intravenous (IV) glucose administration [38].

Intoxication with sympathomimetic agents such as cocaine or amphetamine shares many features with ethanol withdrawal, including signs and symptoms of adrenergic excess. Overdose of monamine oxidase inhibitors, phencyclidine, anticholingergic agents, and lithium, as well as neuroleptic malignant syndrome and serotonin syndrome, may all demonstrate marked agitation and confusion [39]. In the elderly patient, almost any therapeutic drug may be associated with delirium [40]. Withdrawal from other sedative–hypnotics, such as benzodiazepines, barbiturates, GHB, and baclofen, may precipitate a delirium-tremens-like state (see following discussion).

Significant underlying metabolic, traumatic, and infectious disorders should be excluded in the patient with altered mental status associated with ethanol withdrawal. Differentiation may require lumbar puncture, laboratory tests, and computed tomographic scan. These include CNS emergencies, such as intracranial bleeds, meningitis, and encephalitis; metabolic causes, including hypoxia, hypercarbia, sepsis, thiamine deficiency, and sodium and calcium abnormalities; and endocrine disturbances, such as thyroid storm and pheochromocytoma. Distinguishing between delirium tremens and hepatic encephalopathy may be difficult, especially because these conditions often coexist [41].

Management

A successful strategy in treating ethanol withdrawal must address several key goals: alleviation of symptoms, prevention of progression of withdrawal to a more serious stage, avoidance of complications, treatment of coexisting medical problems, and planning for long-term rehabilitation and drug independence [26]. Initial management involves securing the airway, breathing, and circulation. Patients with an altered level of consciousness require oxygen and IV administration of at least 100 mg thiamine and 50 g glucose. The latter two substrates are particularly important, as Wernicke's encephalopathy and hypoglycemia may be confused or coexist with ethanol withdrawal. Severely agitated patients may initially require physical restraints to prevent injury and facilitate sedation. Prolonged use of physical restraints without adequate sedation, however, may be detrimental because agitated patients quite often continue to struggle against their restraints. Such activity perpetuates the risk for hyperthermia, muscle destruction, and resultant myoglobinuric renal failure. Volume resuscitation, correction of electrolyte abnormalities, and vigilance in the diagnosis and treatment of coexisting medical and surgical disorders are vital in reducing morbidity and mortality in the patient with delirium tremens [37,42].

Achievement of adequate sedation is the cornerstone of successful treatment of ethanol withdrawal [43]. Sedation alleviates the excitatory manifestations of withdrawal, prevents progression to delirium tremens, and prevents common complications of agitation, including trauma, rhabdomyolysis, and hyperthermia. Although many agents have been used over the years, benzodiazepines have proved the most effective [43–47]. Benzodiazepines, unlike the neuroleptics, are cross-tolerant with ethanol and function as a replacement drug for the short-acting ethanol, increasing the affinity of GABA for the $GABA_A$ receptor [48].

Diazepam (Valium), chlordiazepoxide (Librium), and lorazepam (Ativan) are the most commonly used parenteral agents. All three drugs can easily be given intravenously to facilitate rapid sedation and titration of effect. Of these agents, only lorazepam has reliable intramuscular (IM) absorption [24,49]. Diazepam and chlordiazepoxide are long-acting agents with active metabolites that prolong their therapeutic effect, avoiding the need for frequent dosing that is associated with shorter-acting agents. Lorazepam, a shorter-acting agent, has no active metabolites and is better tolerated in the elderly and in patients with hepatic dysfunction, producing less sedation. Prolonged therapy (e.g., > 1 month) with high-dose IV lorazepam, however, has also been associated with acute tubular necrosis secondary to the polyethylene glycol used as the lorazepam diluent [50]. Continuous IV infusion of midazolam, a short-acting agent, has also been recommended in the treatment of delirium tremens [51]. However, this approach requires more vigilant monitoring and does not provide the advantages of a long-acting benzodiazepine that is gradually eliminated over several days. Midazolam infusion is also considerably more expensive than therapy with longer-acting agents [52].

The benzodiazepine of choice in the treatment of ethanol withdrawal remains controversial [53,54]. Although many investigators have suggested that lorazepam may be the preferred agent [13,37,55], long-acting benzodiazepines such as diazepam may be more effective in preventing ethanol withdrawal seizures and contributing to smoother withdrawal with less breakthrough or rebound symptoms [56,57].

Symptom-triggered benzodiazepine treatment for alcohol withdrawal is strongly encouraged [58]. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scale is a reliable, validated scale to assess severity of alcohol withdrawal so treatment can be appropriately titrated and individualized. It includes subjective parameters such as anxiety, auditory and visual disturbances, headache, and nausea as well as objective parameters such as tremor, sweating, agitation, and clouding of sensorium. [59] The dose of benzodiazepines needed to achieve adequate sedation varies considerably depending on the patient's tolerance. Although oral therapy may be appropriate in patients with mild withdrawal, those with significant signs of withdrawal require IV treatment. Therapy with an IV benzodiazepine is titrated to the patient's needs by the use of frequent boluses until withdrawal symptoms subside. Using such a front-loading technique helps avoid undertreatment or excessive sedation [60,61]. For example, 5 to 20 mg of diazepam can be administered to the patient every 5 minutes until he or she is quietly asleep but can be easily awakened. Initial safe titration of benzodiazepines requires continual reevaluation by an observer at the bedside. In patients with moderate withdrawal symptoms, a study showed that using a symptom-triggered approach, instead of a fixed-schedule approach, resulted in the administration of less total medication and fewer hours of medication (9 hours vs. 68 hours) [62,63]. A recent study in a surgical ICU demonstrated that this symptom-orientated bolus-titrated approach decreases the severity and duration of alcohol withdrawal symptoms, resulting in reduced medication requirements, fewer days of ventilation, lower incidence of pneumonia, and shorter ICU stay [64].

Failure to obtain adequate sedation with standard doses of the chosen agent should not prompt a switch to an alternative benzodiazepine. Some patients require very high doses to achieve sedation; cases of patients receiving more than 1,000 mg diazepam during 24 hours have been reported [62]. Recent research into GABA receptor physiology suggests that resistance to large doses of benzodiazepines in some patients with alcohol withdrawal may be due to alterations in $GABA_A$ receptor subunits [65]. Chronic ethanol exposure produces upregulation of $GABA_A$ receptor α_4 subunits that are insensitive to benzodiazepines, and downregulation of benzodiazepine-sensitive α_1 subunits. If a patient with severe alcohol withdrawal does not respond to large doses of a benzodiazepine, administration of an alternative agent may be warranted. A drug such as a barbiturate, which acts on the $GABA_A$ receptor regardless of its specific α subunit composition, would be appropriate.

Recent research also suggests that changes in NMDA glutamate receptor physiology may be important in both clinical signs and symptoms of ethanol withdrawal and the excitotoxic neuronal cell death that may occur. In animal studies, NMDA receptor antagonists may attenuate the development of ethanol dependence if administered concomitantly, and may prevent withdrawal seizures and neuronal excitotoxicity if given during periods of withdrawal [20]. Patients who are refractory to high dose $GABA_A$ agonists may potentially benefit from addressing the glutaminergic as well as the GABergic manifestations of ethanol withdrawal. Options here are limited, but drugs such as propofol, which possess both GABA agonist and NMDA antagonist properties, may be particularly helpful.

Adequate early treatment with benzodiazepines usually suppresses significant manifestations of withdrawal and prevents progression to delirium tremens. If delirium tremens is already manifest, sedation with a benzodiazepine does not completely reverse mental status abnormalities. This may be a consequence of the incomplete cross-tolerance of benzodiazepine with ethanol or perhaps the lack of immediate reversibility of some of the CNS effects of withdrawal [66].

Barbiturates, particularly intermediate and long-acting agents such as pentobarbital and phenobarbital, are an alternative class of cross-tolerant sedative–hypnotic agents that can be used in the treatment of ethanol withdrawal [67]. Although excess sedation and a greater tendency to produce respiratory

depression may be more of a concern with barbiturates as compared with benzodiazepines, the drugs are still titrated until the patient is quietly asleep but easily awakened [68]. Phenobarbital dosages more than 20 mg per kg may be required. Withdrawal patients with idiopathic or post-traumatic epilepsy who require maintenance anticonvulsant levels may particularly benefit from this alternative strategy. Phenobarbital may also be useful for those patients who are resistant to benzodiazepine therapy.

Propofol, a sedative–hypnotic agent used for induction and maintenance of anesthesia, has been used successfully for treatment of severe ethanol withdrawal that is resistant to large doses of benzodiazepines (> 1,000 mg per day) [69–71]. Like ethanol, it acts as an agonist at the $GABA_A$ receptor and also inhibits the NMDA receptor. Its onset of action is rapid, it is easily titratable, and sedative effects wear off quickly after short-term use (< 72 hours). The fact that it addresses the glutaminergic as well as the GABAergic aspects of ethanol withdrawal may be one reason for its increased apparent effectiveness in patients resistant to standard therapy with benzodiazepines. Disadvantages of its use include high cost and prolonged sedation when it is used for extended periods [72]. No controlled trials have compared propofol and benzodiazepines for treatment of ethanol withdrawal.

Intravenous and oral ethanol have been used to suppress withdrawal and continue to be used by some medical practitioners, especially surgeons [73,74]. However, IV ethanol intensifies the biochemical abnormalities associated with ethanol metabolism, shifting energy production toward lactate and ketogenesis [75]. The use of ethanol in the treatment of ethanol withdrawal is not recommended [76].

The use of phenothiazines and butyrophenones to treat ethanol withdrawal has been associated with excessive fatalities [42,75,77]. These agents have been shown to lower the seizure threshold, induce hypotension, impair thermoregulation, and precipitate dystonic reactions [78–80]. These drugs have no role in the management of sedative–hypnotic withdrawal [81].

Beta-blockers and central adrenergic agonists have also been promoted as primary agents and as adjuncts to sedative–hypnotics in the treatment of ethanol withdrawal [82]. These agents do not prevent agitation, hallucinations, confusion, and seizures [46,67]. α_2-Receptor agonists such as clonidine and lofexidine act centrally to attenuate sympathetic outflow from the locus ceruleus [15,24]. Although α_2 agonists may help relieve mild withdrawal symptoms such as tremor, diaphoresis, and tachycardia [83,84], there is no evidence that they prevent delirium tremens [85]. A double-blind study comparing oral benzodiazepines (diazepam or alprazolam) to clonidine in the treatment of mild ethanol withdrawal showed that the benzodiazepines were significantly more efficacious in decreasing withdrawal symptoms [48]. A role for sympatholytic agents in management of seriously ill patients has not been demonstrated.

Valproate has been suggested as an alternative or adjunctive treatment for ethanol withdrawal. It appears to potentiate GABAergic neural transmission through a variety of mechanisms, including activation of glutamic acid decarboxylase. Although there is evidence that valproate may be effective in alleviating withdrawal symptoms, further research is needed before it can be recommended for use in ethanol withdrawal [86].

Baclofen is a $GABA_B$ agonist that appears to have a role in the treatment of alcohol withdrawal. In a randomized, controlled trial, it was comparable to benzodiazepines in relieving symptoms of moderate alcohol withdrawal in an outpatient setting [81]. It has also been shown to be more effective than placebo in controlling craving and in inducing abstinence from alcohol. The mechanism for this effect may be due to the influence of $GABA_B$ agonist on the mesolimbic dopamine pathway [82]. Baclofen has not been studied for use in the treatment of alcohol withdrawal in the intensive care setting.

Gamma-hydroxybutyric acid (GHB) is another $GABA_B$ agonist which recent research has suggested may have a role in the treatment of alcohol withdrawal. In randomized, controlled trials, it was comparable to benzodiazepines and clomethiazole in relieving symptoms of moderate alcohol withdrawal in an outpatient setting. Transient vertigo was the most commonly reported side effect, but also occurred with clomethiazole and benzodiazepine treatment. GHB may resolve withdrawal-associated symptoms of anxiety, agitation, and depression more quickly than benzodiazepines, possibly due to its action on dopaminergic and serotonergic neurotransmitter systems [87,88]. This method of treatment is not commonly used, and further study is warranted.

Magnesium sulfate has been suggested as a potential therapy for alcohol withdrawal, but no sound studies have been able to confirm that magnesium supplementation helps alleviate signs or symptoms of alcohol withdrawal, either in normomagnesemic or hypomagnesemic patients [89].

Adequate sedation of the patient with early signs of withdrawal prevents the development of ethanol withdrawal seizures and progression to delirium tremens. Patients who have had an ethanol withdrawal seizure are at risk for progression to delirium tremens and should be sedated with benzodiazepines or barbiturates, as previously discussed. A randomized, controlled trial evaluating patients presenting to the emergency department with ethanol withdrawal seizures and lacking other signs of moderate alcohol withdrawal showed that a one-time dose of lorazepam, 2 mg IV, was more effective than placebo in preventing recurrent ethanol withdrawal seizures [90]. No evidence has been shown to prove that phenytoin is efficacious in the treatment or prevention of ethanol withdrawal seizures [26,91]. Clinical studies failed to show any significant benefit of IV phenytoin when compared with placebo in the prevention of subsequent ethanol withdrawal seizures [92–94].

The use of anticonvulsants to prevent or treat ethanol withdrawal seizures should be limited to patients with an underlying seizure disorder who require maintenance anticonvulsant therapy [29]. These patients often seize at the onset of mild withdrawal secondary to poor compliance with their anticonvulsant regimen and require restoration of adequate serum levels with an anticonvulsant such as phenytoin. Patients who present with an apparent ethanol withdrawal seizure but do not have a history of either underlying seizure disorder or previous ethanol withdrawal seizures require a full seizure workup. For those rare patients in ethanol withdrawal in whom status epilepticus develops, aggressive anticonvulsant treatment is indicated and phenobarbital or phenytoin, or both, can be used in addition to the benzodiazepines. Because status epilepticus and seizures during delirium tremens are rare sequelae of ethanol withdrawal, their occurrence requires a search for underlying traumatic injuries and infection, regardless of any previous history of ethanol withdrawal seizures.

BENZODIAZEPINE WITHDRAWAL

Since their introduction in the early 1960s, benzodiazepines have replaced the barbiturates as the most widely prescribed sedative–hypnotic agents. Initially, these newer agents were not thought to have the same serious withdrawal problems associated with the barbiturates [95]. Subsequent experience has shown that withdrawal from benzodiazepines may be as severe as withdrawal from barbiturates or ethanol. It is estimated that 10% to 20% of adults in the United States use benzodiazepines on a regular basis [96]. The early signs of withdrawal from benzodiazepines are the same as those of ethanol withdrawal. Differences include delayed time of onset, depending on the

duration of action of the agent involved, and the presence or absence of active metabolites. When delayed tachycardia, hypertension, and irritability develop in a hospitalized patient, prior benzodiazepine abuse should be suspected.

Pathophysiology

Signs and symptoms of benzodiazepine withdrawal occur when tolerant patients experience a decline in brain benzodiazepine levels. Individuals who have not developed tolerance do not experience symptoms of withdrawal. Patients who have taken therapeutic amounts of these drugs over an extended period may experience withdrawal (therapeutic dose withdrawal) [97,98], although more commonly it occurs in those who have been regularly taking higher than recommended antianxiety doses. A high daily dose and long duration of benzodiazepine use correlate with a greater risk of developing a moderate-to-severe withdrawal syndrome [96,99]. Although withdrawal usually occurs after abrupt discontinuation of these medications, it may occur to a lesser extent during drug tapering [95]. Iatrogenic benzodiazepine withdrawal has also been described in patients following discontinuation of midazolam-induced sedation in the ICU [100].

Although the mechanisms for benzodiazepine tolerance and withdrawal are not fully understood, it appears that changes in $GABA_A$ receptor subunits, similar to those that occur with chronic ethanol use, may be responsible [101]. Ultimately, a decrease in the availability of exogenous benzodiazepine results in unopposed nervous system stimulation and an increase in agitation and anxiety.

Variability in the time course and severity of withdrawal among the various benzodiazepines can be explained by their differing pharmacokinetics [102]. Drug half-life and the presence of active metabolites correlate with the onset, frequency, and severity of withdrawal symptoms. The onset of withdrawal from shorter-acting agents without active metabolites, such as lorazepam or alprazolam, may be precipitous, with marked symptoms as early as 24 hours after cessation of the drug [103]. Signs of withdrawal from longer-acting agents, such as diazepam, which have a long elimination half-life in addition to active metabolites, may be delayed for 8 days or longer. Withdrawal symptoms from long-acting benzodiazepines may persist for months [104,105]. Concurrent use of other cross-tolerant sedative–hypnotic substances, such as ethanol, barbiturates, chloral hydrate, glutethimide, ethchlorvynol, or meprobamate, along with benzodiazepines increases the probability of developing withdrawal on abrupt discontinuation of these substances.

Administration of the competitive benzodiazepine antagonist flumazenil can result in iatrogenic benzodiazepine withdrawal. Flumazenil is used to reverse sedation in the settings of benzodiazepine overdose, IV conscious sedation, and general anesthesia [106] and was suggested as an adjunct in the weaning of patients from mechanical ventilation [107]. However, flumazenil has not been proved effective in the treatment of benzodiazepine-induced respiratory depression [106]. A history of benzodiazepine use and dependence may not be available when unconscious patients are admitted to the ICU, and benzodiazepine withdrawal with seizures and death has been reported after the use of flumazenil [108–110]. Hence, flumazenil should be used with caution (see Chapter 143).

Clinical Manifestations

Benzodiazepine withdrawal is characterized by CNS excitation and autonomic hyperactivity. Mild early manifestations of withdrawal include psychological symptoms such as anxiety, apprehension, irritability, mood swings, dysphoria, and insomnia. Somatic complaints commonly include nausea, palpitations, tremor, diaphoresis, and muscle twitching.

More severe signs of withdrawal include vomiting, cramps, tachycardia, postural hypotension, and hyperthermia. Significant neuromuscular hyperactivity may be manifested as fasciculations, myoclonic jerks, and seizures [111]. Agitated delirium accompanied by hallucinations and paranoid delusions, and catatonia, have been described [112,113].

In patients taking clonazepam, withdrawal symptoms may develop 3 to 4 days after cessation of therapy. Clonazepam withdrawal may be precipitated or accentuated, or both, by concomitant neuroleptic therapy [114,115].

Diagnostic Evaluation

Benzodiazepine withdrawal may be difficult to distinguish from an underlying anxiety disorder [112]. The time course of the symptoms helps distinguish these two diagnoses. Withdrawal symptoms often worsen rapidly in the early period, followed by gradual improvement and resolution. Unmasked anxiety disorders tend not to deteriorate significantly and persist with time. Perceptual disturbances, not generally associated with underlying anxiety disorders, are commonly found during early withdrawal and may also help distinguish withdrawal from the return of anxiety [104]. These disturbances include paresthesia, tinnitus, visual abnormalities, vertigo, metallic taste, depersonalization, and derealization [98].

Management

Treatment strategies for benzodiazepine withdrawal are similar to those used for ethanol withdrawal. Reinstitution of the drug at a dose that relieves withdrawal symptoms followed by slow withdrawal during 2 to 4 weeks minimizes symptoms and affects the desired decrease in CNS tolerance. Alternatively, a similar cross-tolerant agent can be used. A long-acting benzodiazepine such as diazepam or chlordiazepoxide is preferred. Short-acting agents are disadvantageous because maintenance of therapeutic serum drug levels requires frequent drug administration. In patients with moderate-to-severe symptoms (e.g., seizures, delirium), small IV boluses, such as 5 mg of diazepam, should be given until adequate sedation is achieved. Patients experiencing milder symptoms can be treated by the oral route. Barbiturates such as pentobarbital and phenobarbital can also be used in the treatment of benzodiazepine withdrawal [116,117].

Beta-blockers and clonidine have also been used in the treatment of benzodiazepine withdrawal [118]. Propranolol (10 to 40 mg every 6 hours) may help ameliorate tremor, muscle twitching, tachycardia, and hypertension. However, it has little effect on anxiety, agitation, and dysphoria [96]. Clonidine use has also been advocated, although its efficacy in modulating the intensity, severity, and duration of withdrawal has been questioned [119]. As with ethanol withdrawal, it is important to realize that treating peripheral manifestations of withdrawal may obscure early signs of impending delirium and impedes the assessment of adequate sedation. Phenothiazines and butyrophenones exhibit no cross-tolerance to the benzodiazepines and do not have a role in the treatment of benzodiazepine withdrawal, for the same reasons seen in ethanol withdrawal [120].

Limited data are available on the treatment of flumazenil-induced benzodiazepine withdrawal. Because flumazenil has a relatively short half-life (approximately 1 hour), supportive care should be sufficient in the treatment of mild withdrawal symptoms. The precipitation of seizure activity may require treatment with a benzodiazepine or barbiturate. Due to flumazenil receptor blockade, higher doses of GABAergic agonists may be required.

γ-HYDROXYBUTYRATE WITHDRAWAL

Withdrawal from the commonly abused street drugs GHB or its congeners γ-butyrolactone and 1,4-butanediol (see Chapter 143) may be dramatic and potentially life threatening [121,122]. The pathophysiology is similar to that for benzodiazepine withdrawal. Heavy users of these chemicals report using multiple daily doses (as frequent as every 1 to 3 hours) around the clock [123]. GHB acts as an agonist at GHB and $GABA_B$ receptors. Withdrawal symptoms may include agitation, mental status changes, hypertension, and tachycardia. Other findings are tremulousness, diaphoresis, tachypnea, rigidity, irritability, paranoia, insomnia, and auditory and visual hallucinations [124,125]. High-frequency users appear to be at greatest risk for developing withdrawal delirium after abrupt discontinuation of these agents. Onset of symptoms may begin as early as 1 to 6 hours after the last dose [126]. Severe withdrawal symptoms may persist from 5 to 15 days onward and require prolonged ICU care. Many of these patients require physical restraints and heavy sedation [126]. The use of IV benzodiazepine and other cross-tolerant agents is recommended in the management of these patients. As use and abuse of GHB and its precursors becomes more common, more cases of withdrawal are being reported, including cases in which patients are refractory to large doses of benzodiazepines. Successful treatment of this subset of patients with pentobarbital [127,128] and baclofen [129] has been reported. Barbiturates such as pentobarbital may be helpful because unlike benzodiazepines, they are capable of opening $GABA_A$ chloride channels independently of GABA's presence. Pentobarbital dosages used in case series were 1 to 2 mg per kg IV every 30 to 60 minutes, titrated to improvement in vital signs and altered sensorium. Baclofen's usefulness may stem from the fact that like GHB, it is an agonist at $GABA_B$ receptors, whereas benzodiazepines act only on the $GABA_A$ receptor. One case report describes dosing of 10 mg orally three times daily successfully prevented seizures which occurred every time GHB was withdrawn from a dependent patient.

BACLOFEN WITHDRAWAL

Baclofen is a $GABA_B$ receptor agonist used to treat spasticity resulting from multiple sclerosis or CNS injury. It can be taken orally or delivered by an intrathecal pump, which allows higher CNS levels without the side effects associated with large oral doses. An abrupt discontinuation or decrease in baclofen dose may result in a withdrawal syndrome [130]. The pathophysiology is similar to that for benzodiazepine withdrawal. There are many scenarios in which an intrathecal drug delivery system may fail, including errors in programming the pump or filling the reservoir, development of kinks or occlusions in the tubing, and battery failure.

Onset of withdrawal symptoms may occur within a few hours to a few days after a decrease in baclofen dose. Mild-to-moderate withdrawal symptoms may include increased spasticity, tachycardia, hypertension, fever, neuromuscular rigidity, hyperreflexia, psychosis, and delirium. Severe withdrawal, particularly from intrathecal baclofen, may result in coma, seizures, rhabdomyolysis, hyperthermia, disseminated intravascular coagulation, circulatory failure, delirium, and coma [131–134]. Occasionally, patients may develop a reversible cardiomyopathy. In the most severe cases, multiorgan failure and death may occur [120,121]. The delirium observed with baclofen withdrawal may resemble the altered mental status caused by baclofen intoxication, and baclofen intoxication should always be considered along with withdrawal in the differential diagnosis of delirium in a patient on baclofen. The severe withdrawal syndrome may also mimic other conditions such as infection, serotonin syndrome, and neuroleptic malignant syndrome. In cases such as these, the diagnosis may be easy to miss, and evaluation for pump failure should always be considered. Pump integrity and function may be assessed by plain films, dye studies, nuclear medicine flow studies, port aspirations, or if necessary, operative exploration. Cautiously administering a bolus of baclofen by the pump, by way of lumbar puncture, or by a lumbar drain, and assessing for improvement in 30 to 60 minutes may help confirm the diagnosis. Oral baclofen may also be used, though large doses may be needed and clinical improvement may be delayed by several hours [134].

In addition to supportive care, the most important step in management of baclofen withdrawal is the replacement of the baclofen. Patients who were receiving oral therapy may have the drug administered by nasogastric tube if they are unable to take it by mouth secondary to their withdrawal symptoms. Patients withdrawing from intrathecal baclofen may require high doses of oral baclofen, or may not respond to oral replacement therapy [135]. Replacement oral baclofen doses for intrathecal baclofen withdrawal often range between 10 and 30 mg orally, every 4 to 8 hours [134]. In patients not responding to oral replacement, the reason for pump failure should be identified and remedied, with the previous intrathecal baclofen dose reinstituted [136]. Bolus dosing of baclofen by the pump, by way of lumbar puncture, or by a lumbar drain may be required to initially reverse severe manifestations. If there is any delay in administering baclofen intrathecally in these patients, other sedative medications such as benzodiazepines, barbiturates, or propofol should be provided intravenously. As with oral baclofen dosing and with benzodiazepine treatment of severe ethanol withdrawal, large doses of these agents may be necessary to control severe symptoms, with attention to airway support if the patient is not already intubated. Cyproheptadine (4 to 8 mg orally every 6 to 8 hours) has been suggested as a useful adjunctive therapy in patients with intrathecal baclofen withdrawal who are well enough to take oral medications. More study is needed before this can be definitively recommended. [137].

OPIOID WITHDRAWAL

Opioid withdrawal occurs when a tolerant individual experiences a decline in CNS levels of a chronically used opioid. Unlike withdrawal from sedative–hypnotic agents [138], the manifestations of opioid withdrawal are not usually life-threatening. Recognition of the problem facilitates optimum management of the critically ill patient.

Pathophysiology

Opioid receptors in the locus ceruleus bind exogenous opioids, such as heroin, methadone, or codeine, as well as endogenous opioid-like substances known as *endorphins* and *enkephalins*. Stimulation of opioid receptors reduces the firing rate of locus ceruleus noradrenergic neurons, resulting in the inhibition of catecholamine release [139,140]. The stimulation of inhibitory adrenergic receptors, also found in the locus ceruleus, causes a similar reduction in sympathetic outflow. Chronic opioid use may produce an increase or upregulation of these adrenergic receptors. Subsequent withdrawal of opioids results in increased sympathetic discharge and noradrenergic hyperactivity.

The time course of the withdrawal syndrome depends on pharmacokinetic parameters of the individual opioids [139]. Withdrawal symptoms usually appear about the time of the next expected dose [141]. Withdrawal from heroin, which has

a short half-life, begins 4 to 8 hours after the last dose, whereas withdrawal from methadone, with a long half-life, is delayed until 36 to 72 hours after the last dose. Withdrawal symptoms are more intense if the opioid has a shorter half-life, whereas symptoms are less dramatic but often more prolonged if the abused opioid has a long half-life. Typically, heroin withdrawal peaks at 36 to 72 hours, with symptoms subsiding by 7 to 10 days. Methadone withdrawal may not peak until the sixth day of abstinence and may persist for weeks.

Because prolonged opioid use may be required to facilitate ventilator management in intensive care patients, iatrogenic opioid withdrawal may complicate ventilator weaning [142,143]. Methadone administered by nasogastric tube or subcutaneously has been successfully used to treat these withdrawal symptoms. The use of methadone may shorten the phase of ventilator weaning in these patients.

Clinical Manifestations

Early signs of opioid withdrawal include mydriasis, lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, anxiety, and restlessness [144]. With time, these symptoms may worsen and be accompanied by mild elevation in pulse, blood pressure, and respiratory rate. Myalgias, vomiting, diarrhea, anorexia, abdominal pain, and dehydration accompany more severe withdrawal. Although these patients may become extremely restless, fever and central agitation such as seizures (except in cases of neonatal withdrawal) and mental status alteration are not part of opioid withdrawal. An intense craving for the drug accompanies withdrawal. Recognition of these signs and symptoms in the ICU patient obviates the need for extensive evaluation of the gastrointestinal symptoms and puts clinically puzzling pain complaints in perspective. Appropriate therapy alleviates the patient's discomfort and facilitates management of more pressing ICU problems. After the resolution of most of the objective signs of withdrawal, subjective symptoms, especially dysphoria, may persist for weeks [140].

Opioid withdrawal may occur suddenly in the opioid-dependent patient given naloxone [145]. This iatrogenic withdrawal often occurs after naloxone is given to a patient who is lethargic or comatose and has unrecognized opioid dependency. Naloxone-induced withdrawal may also occur in dependent patients after use of naloxone to reverse the effects of an opioid used during procedural sedation. Vomiting and subsequent aspiration in the unconscious patient are the major complications arising from this problem. This abstinence syndrome is of brief duration due to the short half-life of naloxone, lasting 20 to 60 minutes, and treatment with opioids to reverse the unwarranted effects of naloxone is not indicated. Naloxone, if required, should not be withheld in the dependent patient. A starting dose of 0.04 to 0.10 mg should be used, titrated until the desired effect is achieved or mild signs of withdrawal occur. Coma or hypoventilation that persists after the onset of withdrawal signs is not reversed by administration of additional naloxone.

Naltrexone, an orally active opioid antagonist, induces withdrawal symptoms for up to 48 hours. Nalmefene, another opioid antagonist, may also cause prolonged withdrawal symptoms in the opioid-tolerant patient. A less commonly recognized cause of opioid withdrawal is the use of agonist-antagonist in the opioid-dependent person. Drugs with agonist-antagonist activity include pentazocine (Talwin), nalbuphine (Nubain), and butorphanol (Stadol).

Management

Treatment of opioid withdrawal is a two-tier approach, using cross-tolerant opioid replacement or sympatholytic therapy (e.g., clonidine), or both. The benzodiazepines are not cross-tolerant with opioids. Their role is limited to the management of significant anxiety associated with opioid withdrawal.

Substitution of long-acting methadone for heroin has played a prominent role in the management of opioid addiction [138]. First used in the 1960s for the treatment of heroin addiction [146], methadone was chosen for its chemical similarity to heroin, oral availability, and long half-life (24 to 36 hours). Although the use of methadone for the outpatient treatment of opioid dependence is tightly regulated, physicians do not need special licensing to prescribe methadone to hospitalized patients.

Methadone may be useful in treating the uncomfortable symptoms in patients who depend on any opioid. The dose should be judiciously titrated to relieve symptoms but avoid oversedation. A safe initial dose is 20 mg orally or 10 mg IM. The IM route guarantees absorption in the vomiting patient [144]. Relief of symptoms usually occurs within 30 to 60 minutes when the drug is given parenterally and longer when it is given orally. A second 10 mg IM dose can be given if significant relief is not achieved 1 hour after the first IM dose. Administering 10 to 20 mg by IM route blocks most manifestations of physiologic withdrawal, although some patients may require 20 to 40 mg daily or divided twice per day to avoid psychological withdrawal. In general, dosing to prevent withdrawal symptoms requires considerably less drug than dosing for methadone maintenance. Although withdrawal from opioids should not be attempted during an acute medical illness, once they are medically stabilized, heroin-dependent patients can be tapered with methadone over 1 week. Methadone-dependent patients require 4 weeks or more of gradually decreasing dosages. Notable drugs that interact with methadone, lowering its plasma concentration and potentially precipitating opioid withdrawal, include rifampin and phenytoin [147,148].

For those patients enrolled in methadone maintenance programs, considerably larger doses of methadone are often employed. Some of these patients, particularly early in treatment, may continue to abuse heroin. Higher methadone doses, as much as 150 mg a day or more, have been recommended as a means to reduce concurrent heroin use and retain patients in treatment programs [149,150]. Some community clinics use doses as high as 200 to over 300 mg per day in select patients.

The treatment of pain in patients receiving methadone may require the use of additional opioid analgesia, such as morphine, codeine, or oxycodone. In patients on methadone maintenance, the established maintenance dose may not provide adequate analgesia because of tolerance to the analgesic effects of methadone. Successful pain relief requires the continuation of the methadone maintenance dose supplemented by additional analgesics [151].

Every attempt should be made to minimize significant withdrawal manifestations in the opioid-dependent pregnant patient. Withdrawal in these patients may adversely affect the developing fetus, causing fetal distress and even intrauterine death [152]. Oral methadone maintenance is more compatible with maternal and fetal well-being than continued heroin abuse [153,154] and would likely also decrease the risk of intrauterine acquisition of acquired immunodeficiency syndrome. Cautious treatment of these patients with sufficient methadone to avoid withdrawal may avert these additional complications. After delivery, the neonate must be hospitalized and withdrawn from the drug. In selected pregnancies, lowering the maternal methadone dosage may lead to decreased incidence and severity of neonatal withdrawal [155].

While methadone has been extensively used for decades to help opiate addicted patients circumvent the health problems associated with illicit intravenous drug abuse, there are valid concerns about its safety as well. Methadone is known to cause dose-related respiratory depression and sleep apnea,

which varies greatly based on an individual patient's underlying tolerance. The risk of this increases when methadone is combined with other depressant drugs [156]. Other concerns have increasingly come to light in recent years. Disproportionate numbers of patients on methadone were found to have suffered sudden cardiac death, often without underlying structural heart disease [156]. Though the majority of methadone associated sudden deaths are likely due to respiratory depression, it was also discovered that methadone is a potent potassium channel blocker, especially at higher doses. This prolongs cardiac repolarization (lengthening the QTc interval and predisposing to Torsades de Pointe) [156]. While it is unknown how clinically significant this finding may be, some experts suggest that QTc intervals be checked prior to initiating methadone therapy and be followed during chronic therapy to watch for lengthening of the QTc [156–158].

In recent years, buprenorphine, a partial mu-opioid agonist and K-opioid antagonist, has been increasingly advocated as an alternative to methadone for both maintenance and short-term management of opioid withdrawal [159]. Buprenorphine can be given orally, sublingually, intramuscularly, or intravenously [160,161]. Because of its partial agonist activity, it causes less CNS and respiratory depression and has a ceiling effect, so is less likely to be dangerous in overdose than methadone (though respiratory depression may still occasionally be seen, especially at higher doses, and deaths have been reported). This characteristic also renders it able to block the euphoric effects of heroin and morphine. It produces only a mild withdrawal syndrome when treatment is ceased, but care should be taken when initiating therapy in opioid dependent patients as it may precipitate withdrawal [161]. Of interest, a recent case of deliberate buprenorphine overdose resulted not in respiratory depression but severe opioid withdrawal lasting 4 days [162]. Compared to methadone, opioid withdrawal symptoms may resolve more quickly with buprenorphine but the latter is no more effective when used in the maintenance treatment of heroin dependence [163,164]. Buprenorphine does not seem to have the same propensity to prolong the QT interval as methadone [158]. Buprenorphine has a long half-life (□40 hours), so an additional benefit is that it may be administered every other day or even three times a week as maintenance therapy for opioid addicted patients. Special training and licensing are required for physicians who wish to prescribe buprenorphine or methadone (when used as treatment for opioid dependence) on an outpatient basis.

Sublingual buprenorphine tablets and solution are available as monotherapies as well as in combination with naloxone in a 4:1 (buprenorphine: naloxone) ratio (Suboxone). The naloxone is poorly absorbed sublingually and therefore does not interfere with buprenorphine's effects when taken as directed. Naloxone is added to the buprenorphine to block buprenorphine's euphorigenic effects if an attempt is made to divert the drug for illicit intravenous use (crushing and dissolving tablets etc.).

Sublingual dosing of buprenorphine for opioid dependence maintenance therapy starts with an introductory dose of 2 to 8 mg, based on the patient's degree of neuroadaptation to opioids. Dosing may be to be advanced to 4 to 16 mg on the second day. Over time the dose may be individualized to a range of 4 to 24 mg daily, every other day, or three times a week (though currently this dosing regimen is not recommended) [165]. When initiating buprenorphine therapy, physicians must be alert to the possibility of precipitated withdrawal, and patients should always be prepared for this. Because buprenorphine binds more tightly to the mu-opioid receptor than does heroin or methadone, it knocks any residual drug off the receptor and blocks its agonist effects since buprenorphine itself is only a partial agonist). To minimize this risk, the first dose of buprenorphine should be given at least 6 hours after the last heroin use (ideally once if the patient is already experiencing mild withdrawal symptoms). If the patient is on methadone, the first dose of buprenorphine should be given as long as possible after the last methadone dose (at least 24 hours, longer if the baseline methadone dose is higher) [165]. Precipitated withdrawal symptoms usually start 1 to 4 hours after the buprenorphine dose and last about 12 hours. These symptoms are worst during the first day, but patients transitioning to buprenorphine from methadone may experience mild discomfort and dysphoria for up to 1 to 2 weeks, depending on how much methadone they were using previously. Symptomatic treatment with medication such as clonidine may be employed during this period as needed.

When transitioning from methadone maintenance to buprenorphine, it is recommended that the patient be stabilized on as small a methadone dose as possible (preferably < 30 mg daily) prior to initiating transfer. This minimizes risk of withdrawal and improves success. It is not recommended that patients on 60 mg or more of methadone daily be transitioned. While starting on too low a buprenorphine dose may be insufficient to manage withdrawal, too high a dose increases the risk of precipitated withdrawal. An average starting dose for patients on 20 to 40 mg methadone daily is 4 mg of buprenorphine, with reassessments later in the day or the next day to titrate dose [165]. In addition to maintenance therapy, various tapering opioid detoxification regimens using buprenorphine exist, with starting doses ranging from 1 to 8 mg daily. Therapy may be tapered over 5 to 14 days [161].

Clonidine, a central α_2-adrenergic agonist that binds to the α_2-receptors in the locus ceruleus, is also used to treat opioid withdrawal [166,167]. Stimulation of central α_2-receptors results in feedback inhibition of the norepinephrine activity, decreasing the firing rate of the noradrenergic neurons. These noradrenergic neurons also possess opioid receptors whose stimulation produces a similar reduction in sympathetic activity through the same intracellular messenger system [141]. Clonidine used without the addition of a replacement opioid has been found to be as effective as methadone in treating medically ill hospitalized patients in opioid withdrawal [168]. Clonidine may be administered in doses of 0.1 to 0.2 mg every 4 to 6 hours. Treatment is often continued for 5 to 10 days and then slowly tapered by 0.2 mg per day. Clonidine transdermal patches provide steady-state clonidine levels and may also be useful [151]. Tachyphylaxis to the effects of clonidine may develop by 10 to 14 days [139]. The most concerning side effect of clonidine is hypotension, especially with the first dose. This requires close monitoring. In one study, patients administered buprenorphine–naloxone were more likely to complete a short-term detoxification program and report fewer withdrawal and craving symptoms than those treated with clonidine [169]. The long-term success of this approach is unclear.

Combination therapy with clonidine and naltrexone has also been used for rapid opioid detoxification. Proponents of this approach emphasize the shortened period of withdrawal associated with the addition of naltrexone [170]. Continuing naltrexone as deterrent therapy after opioid withdrawal (akin to the use of disulfiram with alcoholics) has also been advocated, but this approach has a high attrition rate [171]. Delirium has been reported during rapid opioid detoxification of methadone maintenance patients [172].

Administering high doses of opioid antagonists to addicted individuals while under anesthesia has been suggested as a method of achieving detoxification from opiates within 24 to 48 hours. This method, known as ultrarapid detoxification, has been associated with pulmonary and renal failure as well as other complications, including death [173]. Additionally, long-term follow-up has demonstrated relapse of drug abuse in many of these patients [174]. This approach is not recommended.

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FRED A. LUCHETTE

CHAPTER 146 ■ EPISTAXIS

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Epistaxis is a common occurrence in the general population and most frequently is minor and self-limiting. In the intensive care setting, however, epistaxis may further destabilize an already unstable patient and may be life-threatening. Appropriate management of epistaxis requires careful evaluation and management of the patient's hemodynamic status and prompt control of the source of bleeding.

BLOOD SUPPLY OF THE NOSE

The internal and external carotid arteries, with frequent free anastomoses within the nasal mucosa, provide a rich blood supply to the nose, and venous drainage parallels the arterial supply.

The internal carotid artery (ICA) supplies the nasal mucosa through the ethmoid branches of the ophthalmic artery. The ophthalmic artery, the first branch off of the ICA, enters the orbit through the optic canal and divides into anterior and posterior ethmoidal branches. Both anterior and posterior ethmoidal arteries exit the orbit through the medial orbital wall at the level of the frontoethmoid suture line, an important landmark in the operative management of epistaxis originating from these vessels. These arteries then pass medially through the roof of the ethmoid sinuses and enter the anterior cranial fossa, from which they descend through the cribriform plate to enter the nose. The anterior ethmoidal artery, the larger of the two, supplies the anterior nasal septum and lateral nasal wall. The posterior ethmoidal artery supplies the region of the superior turbinate and corresponding portion of the septum.

The external carotid artery (ECA) supplies the nose through two of its terminal branches, the facial artery and the internal maxillary artery. The facial artery, a major branch of the external carotid system, providing blood supply to most of the lower face and lips, supplies the superior labial artery, which enters the nose lateral to the anterior nasal spine and supplies the anterior nasal septum (Figs. 146.1 and 146.2).

The maxillary segment of the internal maxillary artery (IMA) is the primary contributor to the nasal blood supply, crossing the infratemporal fossa to the pterygopalatine fossa. At this point, it divides into multiple terminal branches that supply the nasal cavity primarily by the sphenopalatine artery (SPA). The SPA enters the nasal cavity through the sphenopalatine foramen at the lateral nasal wall posterior to the horizontal portion of the middle turbinate, and divides into multiples branches that supply the posterior septum, lateral nasal wall, and sinuses (Fig. 146.3).

On the anterior nasal septum lies *Kiesselbach's plexus* or *Little's area*, an abundant plexus of vessels consisting of the most prominent anastomoses between the external and internal carotid artery systems. It is at this region that anterior epistaxis most frequently originates, reported in up to 90% of cases [1,2]. Posterior epistaxis, on the other hand, most frequently occurs near the sphenopalatine foramen from branches of the SPA, frequently a result of prior surgery or trauma.

CAUSES OF EPISTAXIS

Risk factors and causes of epistaxis may be divided into local and systemic etiologies (Table 146.1).In the intensive care unit (ICU) setting, epistaxis usually results from a combination of these etiologies; however, direct nasal trauma still plays a central role in its development. Trauma may result from digital manipulation by the patient or nasal fractures with subsequent mucosal disruption; however, in the ICU, nasal trauma is often iatrogenic from nasal oxygen, continuous positive airway pressure (CPAP), or particularly from nasal tube placement (nasogastric feeding tubes, nasal endotracheal tubes, etc.). Nasal cannulas in particular cause bleeding as a result of mucosal abrasions or mucosal drying from non-humidified high flow oxygen. A humidified face mask or face tent is preferred in particularly high-risk patients (history of epistaxis, long-term anticoagulation). Simply moving a nasal tube to the contralateral side may minimize or prevent progression of traumatic epistaxis resulting from tube placement.

Other causes of mucosal dryness include overuse of nasal decongestants or cocaine. Alterations in nasal airflow with subsequent drying may result from congenital or acquired anatomic abnormalities such as septal spurs and deviations, as well as septal perforations (which can themselves be caused by the potent vasoconstrictive effects of drugs such as cocaine). Epistaxis occurs more frequently during the winter months, presumably because of the lower humidity in ambient air. Because factors such as mucosal dryness and trauma most frequently affect the anterior nose, most epistaxis is anterior in nature.

Systemic factors and preexisting conditions place ICU patients at particularly high risk for epistaxis. Studies show that up to 45% of patients admitted for epistaxis have a comorbid condition that could cause or exacerbate bleeding [3]. Literature has identified patients older than 50 years as being particularly predisposed to severe epistaxis refractory to local measures of control, likely due to the effects of endothelial degeneration, atherosclerotic changes, and other systemic conditions. These include hypertension, atherosclerotic vascular disease, coagulopathies, and conditions requiring antiplatelet or anticoagulative medications (aspirin, clopidogrel, heparin, warfarin) such as deep vein thrombosis (DVT), pulmonary embolus (PE), cardiac arrhythmias, coronary artery disease (CAD), and vascular stent placement. Medications such as these all affect coagulation and may subsequently result in recurrent or refractory episodes of nasal bleeding. However, the conditions for which these agents are used present a particular challenge, as stoppage of these medications can be life-threatening.

Coagulopathies such as von Willebrand disease and hemophilia must be considered in patients with recurrent or refractory disease. Failure to identify these conditions may result in a delay in administration of medical therapies such as factor VIII or desmopressin acetate that can aid in reversing the underlying disease process.

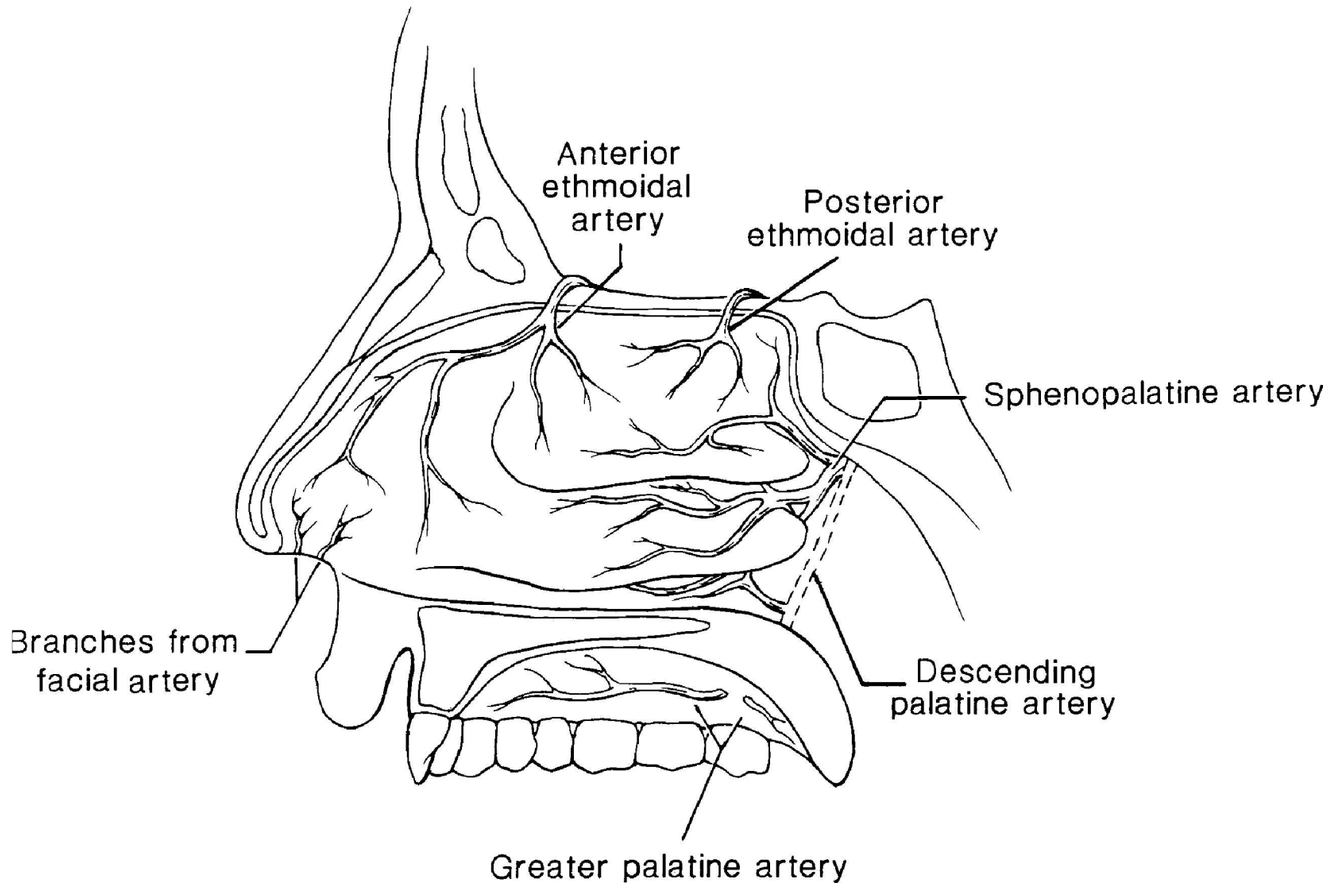

FIGURE 146.1. Blood supply of the lateral nasal wall.

In the ICU setting, it is most often a combination of a number of the above factors that results in epistaxis. Identifying and addressing the various contributing factors is of central importance when managing epistaxis in the ICU.

MANAGEMENT

Initial evaluation of the ICU patient with epistaxis should first and always be guided by the rules of *A*irway, *B*reathing, and *C*irculation, with a quick determination of the severity of the bleed. In case of a severe bleed in an unstable patient, the airway should be secured (by intubation) and two large bore intravenous (IV) lines should be placed if not already established. If the patient already has a tracheostomy tube in place, the cuff should be inflated to prevent passage of blood products and protect the airway. Frequent suctioning of the pharynx can assist in reducing aspiration. Once the airway is secured and hemodynamic status addressed, efforts can be focused on the control of bleeding. Typically, most patients are hemodynamically stable and are able to protect their airway, allowing for a more thorough examination.

In patients who are hemodynamically stable, a short and focused history, including information regarding nasal trauma, duration, and amount of blood loss is invaluable. After the severity has been assessed, one can discern laterality, history of coagulation and hemodynamic disorders, and iatrogenic factors that may be contributing. In the ICU setting, patients are frequently unable to provide a history such that nursing, family members, and other ancillary staff are needed to provide crucial information. It is also necessary to determine if a bleed is originating anteriorly in the nasal vault or more posteriorly (e.g., copious amounts of expectorated blood, hematemesis), which is typically more severe and is not easily stopped with local pressure or topical cauterization. One must exercise caution when suctioning the nasopharynx to avoid dislodgment of clot into the hypopharynx and larynx, which may result in airway compromise.

Vital signs should be assessed and hypertension controlled to reduce the bleeding. The nasal examination may then be undertaken, best accomplished with good lighting, a nasal speculum, and suction. If a discrete source of bleeding is easily visualized, then local coagulation with silver nitrate applicators may suffice. However, diffuse bleeding is often noted, and a vasoconstrictive agent such as oxymetazoline or phenylephrine may be sprayed to decrease bleeding and improve visualization.

The first step in attempted control of epistaxis should consist of a topical vasoconstrictive agent (oxymetazoline or phenylephrine) sprayed liberally on the side of bleeding (if localized) or bilaterally, followed by uninterrupted external digital pressure for 15 to 20 minutes. Pressure should be applied with a tight pinch, compressing the nasal alae against the nasal septum in such a manner as to prevent passage of nasal airflow. During this time, the oropharynx should be examined to evaluate for

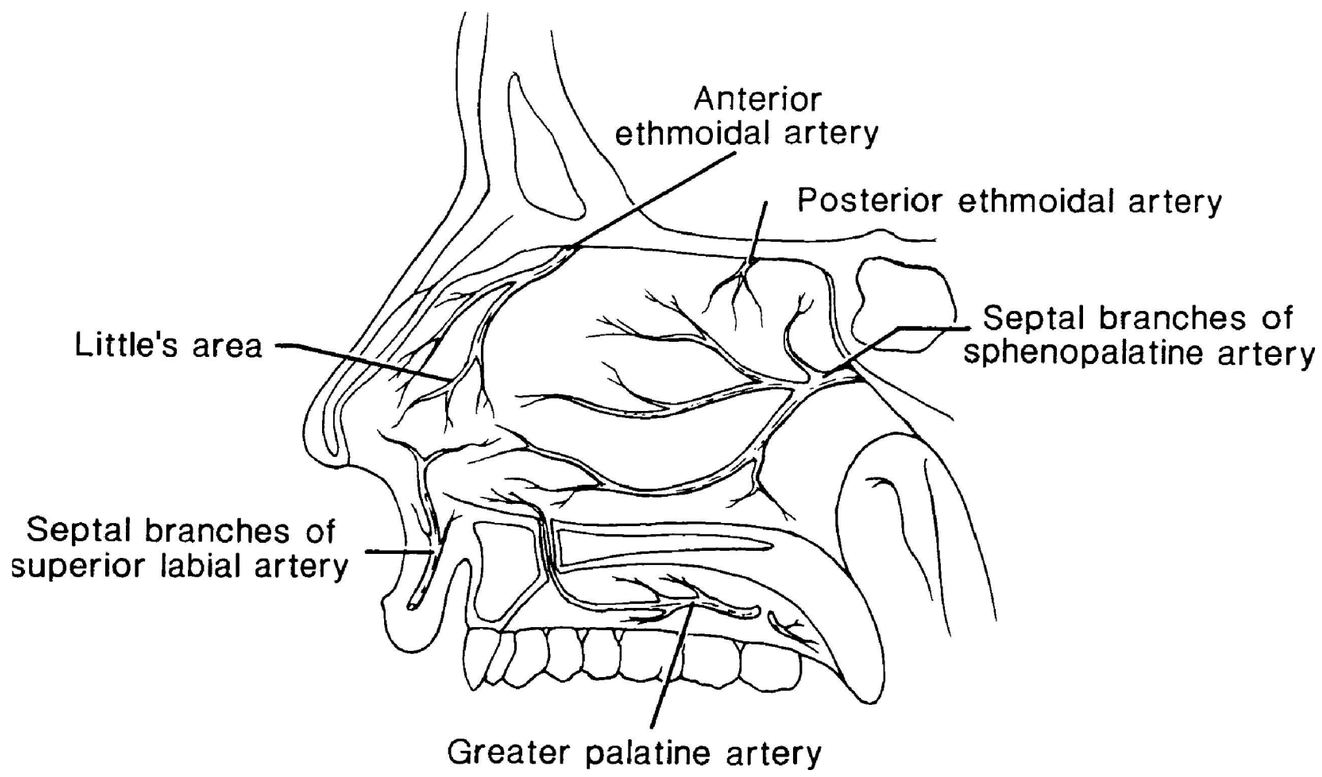

FIGURE 146.2. Blood supply of the nasal septum.

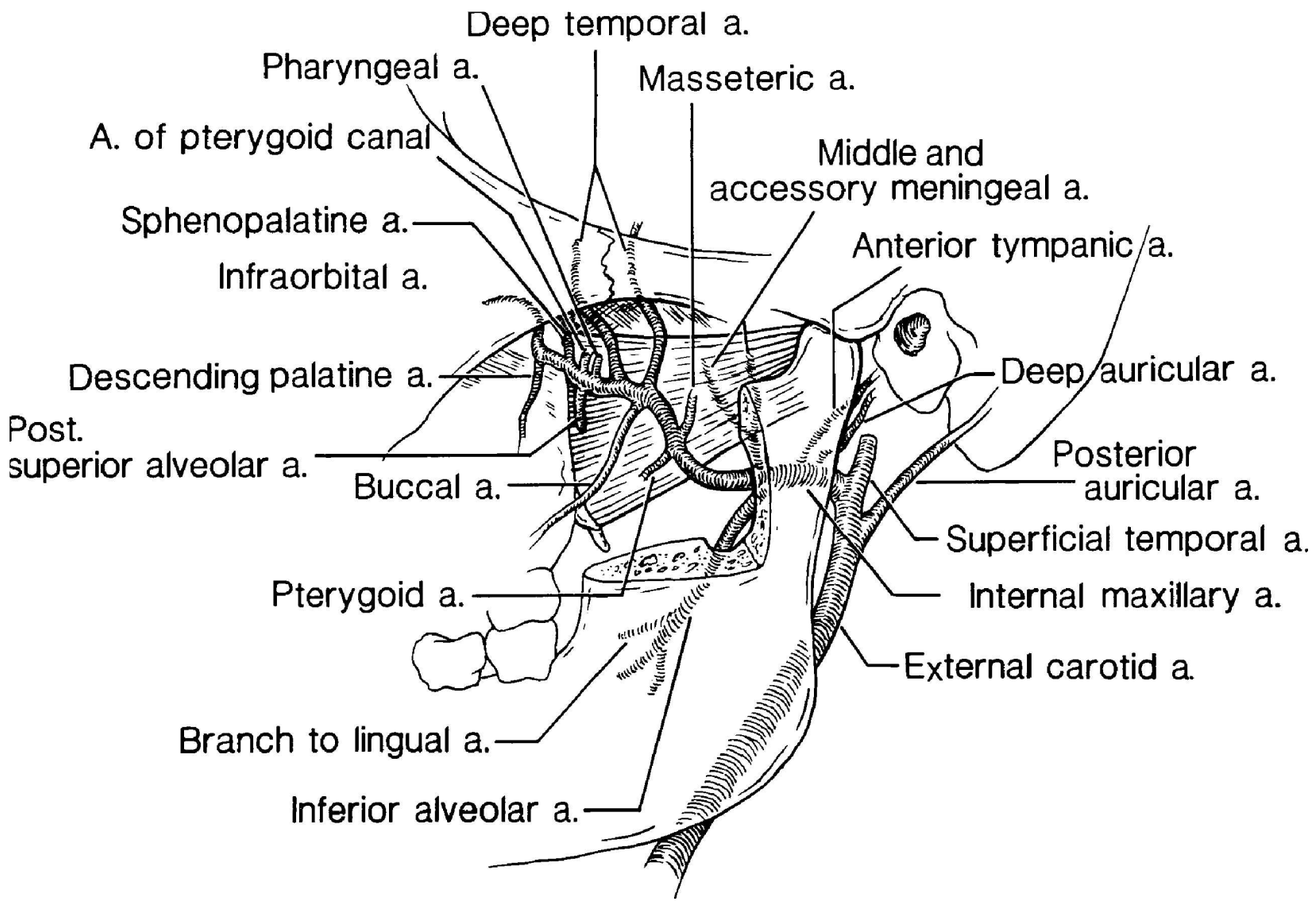

FIGURE 146.3. Course and branches of the internal maxillary artery.

continued bleeding, which may raise suspicion for a posterior source. One should be aware that only minimal anterior bleeding may occur with significant posterior epistaxis.

Because the majority of bleeding is anterior on the septum, a topical vasoconstrictive agent and external pressure will frequently achieve hemostasis and is sometimes all that is necessary. Krempl et al. found that up to 65% of cases of epistaxis were controlled with a topical vasoconstrictor and pressure alone [4]. If these measures are successful, measures should be taken to decrease mucosal drying and subsequent recurrence, including placement of a humidified face tent, topical vasoconstrictive agent twice daily for a maximum of 5 days (to prevent complications such as rebound nasal congestion and septal perforation), frequent topical saline sprays, application of lubricating ointment (e.g., neomycin/polymyxin) to the nasal septum twice daily, and control of hypertension.

Laboratory tests should be considered in patients with significant or recurrent epistaxis. A complete blood cell count, coagulation studies, and a bleeding time should be performed. In patients with severe bleeding or those who are severely anemic, one should consider a crossmatch with the initial blood draw due to the time necessary to prepare blood products. Liver function tests may help elucidate the cause and identify patients with coagulopathies as a result of impaired hepatic function.

TABLE 146.1

ETIOLOGIES OF EPISTAXIS

Local factors	Systemic factors
Anatomic Septal deviation, Septal spur Septal perforation	Hypertension[a]
Trauma[a] Digital/nose-picking Nasal/facial fractures Nasal tube placement (nasogastric, nasotracheal, etc.)	Coagulopathy[a] Hepatic dysfunction Disorders of platelet function/aggregation (e.g., von Willebrand disease) Hematologic malignancy Hemophilia
Mucosal dryness[a] Cold weather Nasal cannula use CPAP Chronic intranasal corticosteroid use Nasal decongestant overuse Cocaine abuse	Medication effect[a] ASA Clopidogrel Warfarin Heparin
Sinonasal infection/ inflammation	Vascular disorders Wegener's granulomatosis Churg-Strauss syndrome Hereditary hemorrhagic telangiectasia
Nasal polyposis	Drug abuse (e.g., cocaine)
Intranasal mass Arteriovenous malformation Malignancy	Alcohol abuse
Foreign body	Renal failure
Recent nasal/facial surgery	Malnutrition

[a]In ICU patients, epistaxis most commonly results from a combination of these factors.

Cautery

The majority of nosebleeds arise from Kiesselbach's plexus on the anterior nasal septum, and cauterization may be performed either with silver nitrate applicators or electrocautery to the bleeding site if unresponsive to topical vasoconstrictors and pressure. In stable patients with mild to moderate bleeding, a nasal endoscope (0-degree telescope with light source) can aid in visualizing bleeding sites and focus cauterization more precisely on the source, but a nasal speculum remains a viable alternative. In the awake patient, topical anesthesia should be used (such as 4% lidocaine or tetracaine) that may be mixed with the topical vasoconstrictor being applied, to decrease pain and improve examination conditions. Silver nitrate, when in contact with water in blood, precipitates and is reduced to neutral silver metal, which releases reactive oxygen species to coagulate tissue. Silver nitrate use is useful for minor bleeds, but may be inadequate with more severe bleeds as heavy blood flow washes away the silver nitrate before it can act.

Overly aggressive cauterization or bilateral cautery should be avoided to prevent ulceration, which may subsequently cause re-bleeding or result in a septal perforation in the long term. Injudicious cautery may also lead to synechia (scar) formation between the septum and the turbinate/lateral nasal wall,

which can later impair the patient's breathing and result in abnormal airflow.

An additional tool in initial control in patients with evidence of significant posterior bleeding includes transpalatal vasoconstriction of the sphenopalatine artery, utilizing a 25-gauge needle bent at 2.5 cm and injecting 1 to 2 mL of 1% lidocaine with epinephrine (1:100,000) in the descending palatine foramen, located just medial to the upper second molar. This procedure may slow bleeding enough to allow for improved examination [5].

Nasal Packing

Nasal packing, which is typically described as anterior or posterior, should be considered as the next step in management after failure of local and medical measures such as external pressure and cautery. Packing can also be used in cases where the source of bleeding is not evident on physical examination, or when the bleeding is severe and must be temporized until further definitive management can be performed.

Anterior Nasal Packing

Anterior nasal packing is generally performed for epistaxis originating from the anterior nasal cavity to tamponade the vessel at the source, as well as to provide coverage of the bleeding site, allowing the primary stages of healing to occur in the absence of further local trauma and desiccation that can result in re-bleeding. As most epistaxis occurs anteriorly, this form of packing is usually sufficient. Many different types of packs are now available, utilizing a variety of both absorbable and nonabsorbable materials. The choice of anterior packing material is based on clinician preference and comfort level, as well as product availability in the hospital.

Common absorbable materials used for anterior packing include gelatin foam (e.g., GelFoam®-Pfizer, Inc, New York, NY) and oxidized cellulose (e.g., Surgicel®-Ethicon, Inc, Somerville, NJ), which encourage platelet aggregation and protect bleeding sites from further trauma and desiccation. Other materials include microfibrillar collagen (e.g., Avitene©-Davol Inc, Cranston, RI) and thrombin-gelatin combinations (Floseal®-Baxter International, Deerfield, IL) that can be instilled in the nasal cavity as a slurry. The advantages of these products include their ease of use, decreased patient pain, elimination of the need for pack removal, and improved conformity to the irregular contours of the nasal cavity. However, these products may not be effective in control of brisk arterial bleeding as they apply only low pressure to the nasal mucosa, and they are significantly more expensive than traditional packs.

Traditional nasal packing has involved the use of 0.5-in by 72.0 petroleum jelly strip gauze, layered with a bayonet forceps from inferior to superior along the length of the nasal cavity (Fig. 146.4). Over the years, the use of nonabsorbable sponges composed of hydroxylated polyvinyl acetate that expands when wet (e.g., Merocel® Medtronic Inc, Mystic, CT) has gained popularity due to their ease of use and applicability by hand without the need for additional instruments. The sponge is coated in antibiotic ointment prior to placement primarily for lubrication to ease application and decrease further septal trauma, but there is no published evidence to support a decrease in infectious complications [5,6]. Using a bayonet forceps or by hand, the sponge is then placed in the nasal cavity on the side of bleeding, sliding along the nasal septum to avoid the turbinates and ensure tamponade of the septal bleeding source. The packing should slide easily and should not require a high degree of force to decrease further mucosal trauma. Once in place, the sponge is copiously impregnated with a vasoconstrictive agent or sterile saline. Subsequent swelling of the sponge provides high pressure against the site of bleeding resulting in hemostasis. At this point, the oropharynx should be inspected to evaluate for continued bleeding posteriorly. Persistent anterior bleeding around the pack may necessitate repositioning or augmenting the pack. Anterior nasal packing has been shown in randomized, controlled trials to successfully control bleeding in up to 80% of cases [7,8]. The use of the Merocel® has published success rates up to 92% [9].

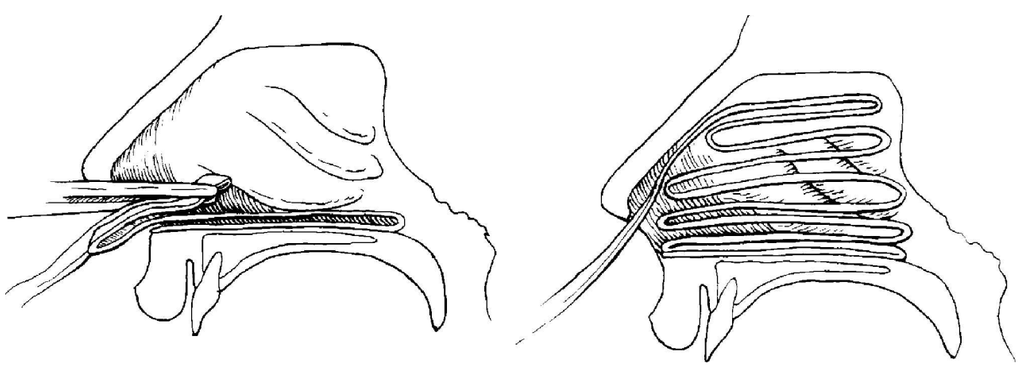

FIGURE 146.4. Correct placement of an anterior nasal pack.

Posterior Packing

After anterior packing is applied, continued postnasal bleeding should necessitate placement of a posterior pack. Posterior epistaxis is seen more frequently in elderly patients and patients with a history of prior sinus surgery or craniofacial trauma, systemic disorders, and prior nosebleeds [10]. The incidence of posterior epistaxis is, therefore, greater in ICU patients. Because of the often severe nature of the bleeding and relative inaccessibility of the source, conservative measures with pressure and cauterization as well as anterior packing have a limited role in the control of posterior epistaxis. The sphenopalatine artery is a large-caliber vessel, and the blood loss from an episode of posterior epistaxis is often significant, such that consideration should be given to blood transfusion as indicated. Posterior packing is also used as a temporizing measure to slow bleeding in anticipation of surgical management.

The classic posterior nasal packing consists of rolled gauze or tonsil packs secured in the posterior choanae by inserting the pack through the oral cavity and then into the nasopharynx by sutures through the nose (Fig. 146.5). Although very effective, this is difficult to perform, time consuming, and painful for the patient, and it is rarely performed today.

A more commonly used method of posterior nasal packing utilizes a Foley catheter (12 or 14 French) with a 30-mL balloon, readily available in the ICU setting. The nose is first cleared of any previously placed packs, debris, or clots, and topical anesthesia with a vasoconstrictor is applied. With the balloon deflated, the Foley catheter is inserted through the involved nares into the nasopharynx. One may examine the posterior oropharynx to confirm that the tip of the catheter has been placed entirely through the nasal cavity. The catheter is inflated with 10 to 20 mL saline and then pulled anteriorly to wedge the balloon snugly into the posterior nasal cavity and choanae (Fig. 146.6). The oropharynx is again examined to ensure that the soft palate is not displaced or engaged by the balloon, as this may lead to palatal necrosis. While the catheter is held under tension, anterior nasal packing is placed as above. The Foley catheter is then secured against the anterior nasal packing (extending out of the involved nares) using an umbilical cord clamp to maintain pressure and prevent posterior migration of the balloon into the pharynx. The clamp should be rotated periodically to reduce the occurrence of alar and columellar necrosis (additional padding may be placed), and the area must be checked frequently for this complication.

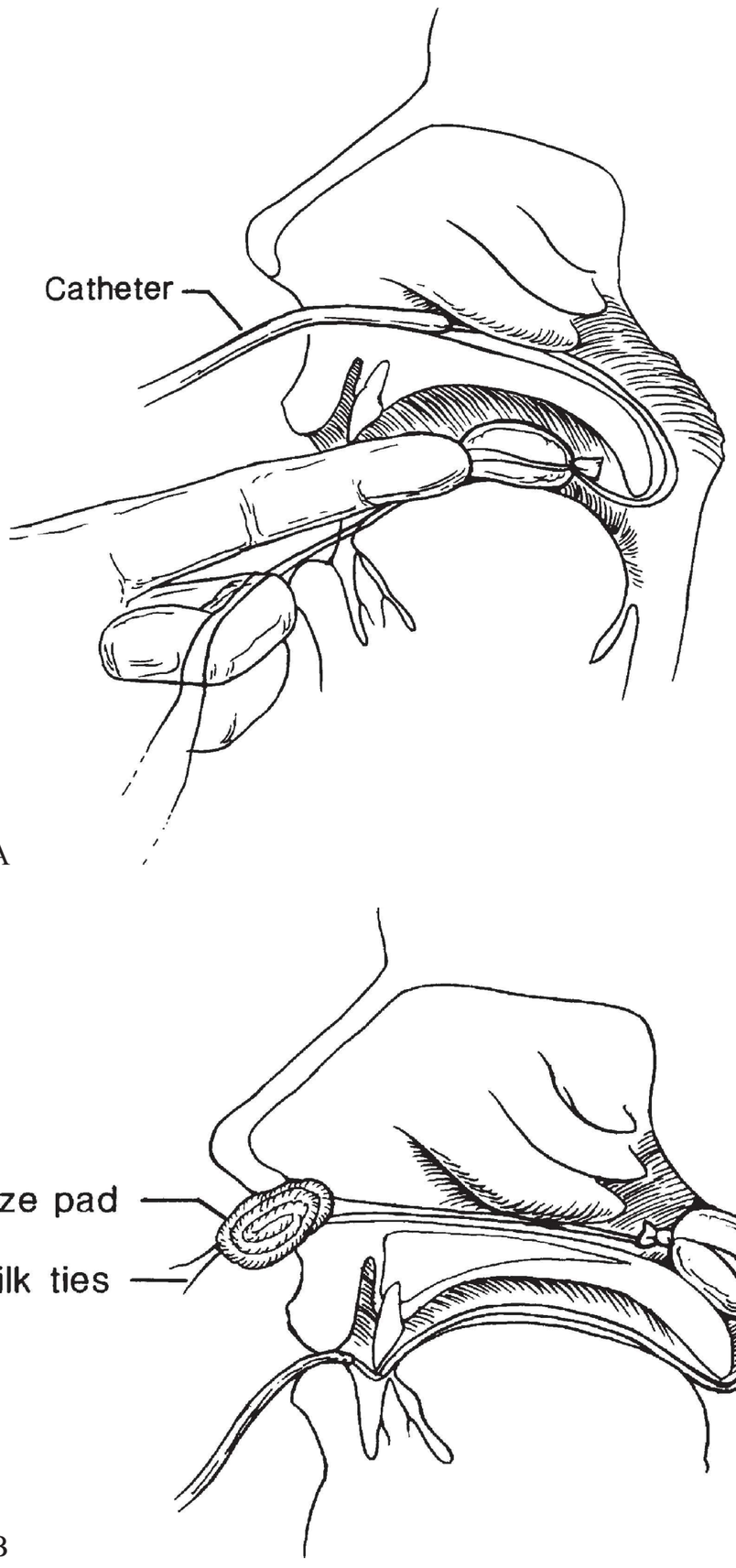

FIGURE 146.5. A,B: Insertion of a nasopharyngeal (posterior) pack (traditional method).

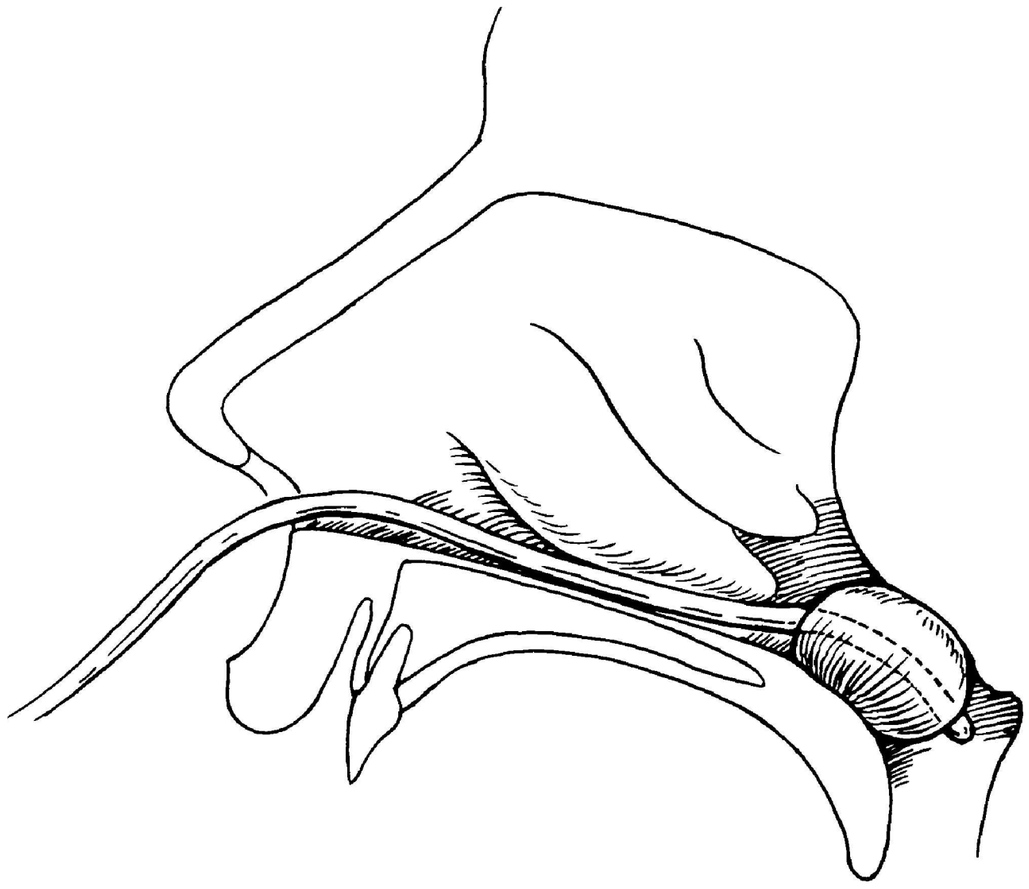

FIGURE 146.6. Foley catheter with balloon inflated.

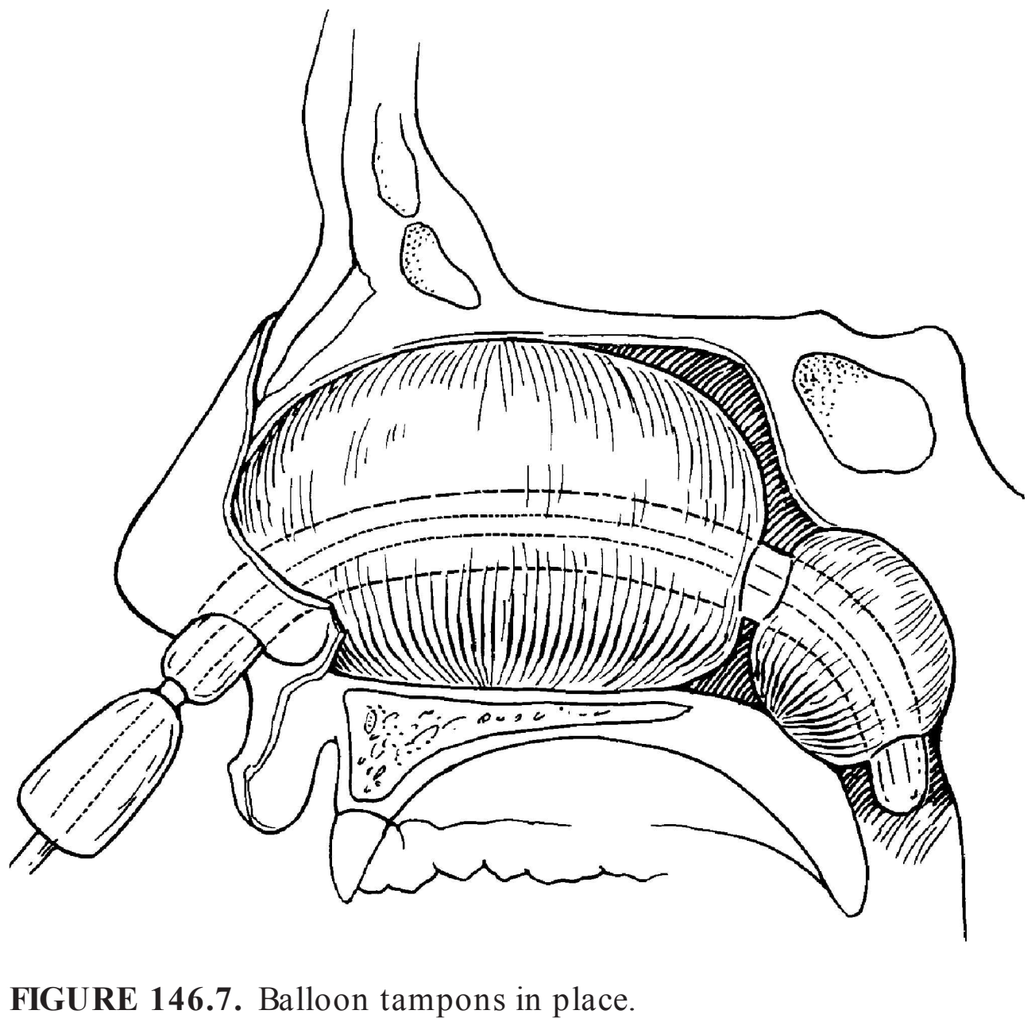

FIGURE 146.7. Balloon tampons in place.

Additional options for posterior nasal packing include balloon tampons designed for this purpose (Fig. 146.7). These devices consist of a catheter with two balloons: one that inflates in the choanae and a second that inflates in the nasal cavity. Although easy to insert, the balloons do not conform to the contour of the nasal cavity and consequently may fail. If bleeding persists, a classic posterior pack should be placed.

Complications associated with the posterior nasal pack may be serious, and all of these patients should remain hospitalized and monitored. Pulmonary compliance may be impaired through a postulated "nasopulmonary reflex" ("diving reflex"), of questionable clinical significance, which may result in apnea, hypoxia, and dysrhythmias [11,12]. All patients with posterior packs are hospitalized and monitored, and unstable or unhealthy patients should be admitted to the ICU. Eating is impaired by a posterior pack, and strong consideration should be given to keeping the patient NPO. The airway may become compromised, and intubation or rarely tracheostomy may be necessary. In addition, the procedure is often painful due to pressure on the posterior septum and choanae, and alar necrosis may result from pressure anteriorly. Posterior nasal packing alone has been shown to have a success rate of up to 70% for control of bleeding, a modest figure considering the aforementioned risks and potential complications [13,14]. As a result, additional measures have gained support in the treatment of posterior epistaxis, as later described.

MANAGEMENT AFTER PACKING

Once the patient's condition has been stabilized and bleeding controlled, attention should be redirected to the patient's general state. If the bleeding was significant, the blood cell count should be checked and the patient transfused as needed with ample additional units available. Coagulopathies and hypertension should be addressed and reversed, and other factors that may aggravate bleeding should be corrected. Adequate pain control should be provided.

In general, packing is left in place for 3 to 5 days to permit the patient's condition to stabilize and adequate primary healing of the source of bleeding. The decision of when to remove packing in an ICU patient is also influenced by the patient's comorbidities, which should be aggressively

controlled/minimized. Antibiotics with adequate *S. Aureus* coverage (e.g., cephalexin, clindamycin if penicillin allergy) should be used while nasal packing is in place to decrease the bacterial load that accumulates on the packing and prevent a life-threatening toxic shock syndrome. If antibiotic-impregnated gauze packing is used, the incidence of clinically significant secondary infections is quite low, and antibiotics may not be needed in immunocompetent, stable patients [12]. It is also important to minimize the amount of time that packing is used in immunocompromised individuals because of their increased susceptibility for infections.

If a posterior nasal pack is used, utilizing a balloon in the choanae, it should be slowly deflated prior to removal. If bleeding recurs, the balloon can be reinflated and left in place longer. If repeated attempts at removing nasal packing are unsuccessful, arterial ligation or embolization must be considered. Endoscopic-guided cauterization may be effective in controlling persistent localized bleeding [15].

ARTERIAL LIGATION

If nasal packing fails to achieve control of bleeding, or if the patient has had multiple episodes of epistaxis, arterial ligation may be warranted. In an extreme situation in which a patient is having life-threatening epistaxis, ligation of the external carotid artery decreases the nasal blood flow and can be life saving but does not result in long-term control of bleeding [16]. If the bleeding is localized to the anterior/superior nasal cavity, consideration should be given to ligation of the ethmoidal arteries. Most often, the bleeding is diffuse, and the ethmoidal arteries are ligated together with the sphenopalatine artery.

Angiographic arterial embolization of the ethmoidal arteries is not advised due to the risk of blindness and stroke, and they must therefore be ligated surgically, which drastically reduces these risks [17]. The ethmoidal arteries are approached through the external ethmoidectomy ("Lynch") incision made halfway between the medial canthus and the nasal dorsum. The vessels are identified along the frontoethmoid suture line as they leave the orbit and enter the ethmoid sinus. Once identified, the arteries are ligated with clips or suture [18]. The relationship of these vessels to the lacrimal crest and optic nerve is critical because the posterior ethmoidal artery lies just a few millimeters from the optic nerve, and severe iatrogenic complications can result if the anatomy is not respected.

Ligation of the sphenopalatine artery in the treatment of posterior epistaxis may be performed using an open or endoscopic approach. However, endoscopic techniques are being performed with greater frequency due to its equal efficacy and decreased morbidity when compared to the open Caldwell-Luc procedure. It has even been shown to have a role in treating patients with severe epistaxis and coagulopathies [19]. Transnasal endoscopic sphenopalatine artery ligation (TESPAL) is performed under general or local anesthesia using a nasal endoscope to identify the sphenopalatine artery and its branches at the sphenopalatine foramen. Endonasally, an incision is made with a sickle knife just anterior to the crista ethmoidalis under the middle turbinate, and a mucoperiosteal flap is raised. As the crista ethmoidalis is encountered, the vessels are identified leaving the sphenopalatine foramen posteriorly, and vascular clips and/or cautery are applied under direct vision. Complications include palatal numbness, sinusitis, decreased lacrimation, and septal perforation; however, control rates are reported up to 87% to 100% [20,21].

The traditional open approach involves clipping the internal maxillary artery (prior to the SPA) in the pterygopalatine foramen through the maxillary antrum. A Caldwell-Luc approach is undertaken (intraoral sublabial incision for access to the anterior face of the maxillary sinus), and the anterior wall of the maxillary sinus is partially removed. The posterior wall of the sinus is then breached and the pterygopalatine fossa entered. The internal maxillary artery and its branches are identified and locking clips placed. The vessels themselves are not transected. Complications of this procedure include facial and buccal numbness and discomfort (from potential infraorbital nerve transection), sinusitis, oroantral fistula, and chronic pain. Failures can occur in up to 40% of cases due to difficulty in identifying the internal maxillary artery, incomplete vessel ligation, formation of anastomoses distal to the ligation (e.g., in the descending palatine artery), and persistent hypertension [14].

After the arteries are ligated, any nasal packing is removed and the nasal cavity is examined for persistent bleeding. If bleeding is present, endoscopic cauterization should be attempted, as well as further medical evaluation for an uncorrected coagulopathy.

ARTERIAL EMBOLIZATION

Selective angiography with embolization of source vessels has compared well in the literature with other invasive techniques for management of refractory epistaxis, with success rates reported from 80% to 90% [20,22]. It may be performed prior to or after surgical management in the event of failure, and presents a treatment option for patients who are very poor operative candidates. However, the procedure is dependent on the availability of an experienced interventional neuroradiologist. As noted earlier, embolization cannot be performed for epistaxis in the superior nasal cavity in the region supplied by the ethmoidal arteries, as these vessels arise from the ICA and ligation could have devastating consequences including blindness or stroke. The internal maxillary artery, however, arises from the ECA, and embolization is a viable option. The procedure is performed using a single femoral puncture, usually under local anesthesia. After diagnostic carotid angiography is performed, the catheter is advanced into the IMA, and embolization is performed with Gelfoam®, coils, or polyvinyl alcohol particles. Often the vessels are embolized bilaterally to decrease the likelihood of development of collateral circulation and re-bleeding, reported in 10% to 20% of cases. Complications are similar to those for any cerebral angiography and include stroke (reported in up to 4% of cases), blindness, temporofacial pain, and renal abnormalities due to contrast loads.

SURGERY, EMBOLIZATION, OR PACKING?

Data remains controversial regarding which is the superior treatment modality for epistaxis: arterial ligation or embolization, both of which are employed when local cautery or nasal packing has failed. Patients with bleeding from the ethmoidal artery region (anterior epistaxis) are better served by surgery due to the risks associated with embolization of the internal carotid artery system. However, bleeding from the SPA/IMA region (posterior epistaxis) may be treated by either or both modalities.

Although both approaches have been shown to control bleeding in up to 85% of patients [23–25], multiple case series reports have found surgical arterial ligation to be equal to or better than embolization in terms of success rate [20,22]. Patients not stable enough to tolerate general anesthesia may benefit from embolization, which does not require general anesthetic but does expose the patient to the risks of angiography. Skilled personnel are required for either technique. Goddard and Reiter showed that there were no differences in length of

TABLE 146.2

SUMMARY OF EVIDENCE-BASED TREATMENT RECOMMENDATIONS IN THE MANAGEMENT OF EPISTAXIS

Intervention	Year	Study	No. of patients	Findings	Reference
A. Medical/nonsurgical management					
Hold warfarin (if applicable)	1997	Prospective	20	No decrease in bleeding or effect on hospital stay	Srinivasan, et al. [41]
Oral ice pack placement	1991	Prospective	16	Decreased nasal mucosal blood flow	Porter, et al. [42]
Intranasal topical antiseptic	1999	RCT	22	Topical is equal to silver nitrate cautery in control	Murthy, et al. [43]
Intranasal topical lubricant + steroid	1999	Prospective	100	Resolution of symptoms in 89% of chronic bleeds	London, et al. [44]
Oxymetazoline as initial therapy	1995	Retrospective	60	Effective as sole therapy in 65% of patients	Krempl, et al. [4]
Oxymetazoline for posterior epistaxis	1999	Retrospective	36	All cases resolved with initial or repeat doses only	Doo, et al. [45]
Iodoform gauze pack versus Merocel	1995	RCT	50	No significant difference in controlling epistaxis, Merocel more comfortable and easier to insert	Corbridge, et al. [46]
Merocel as initial therapy	1996	Retrospective	83	Effective in controlling epistaxis in 91.5% alone	Pringle, et al. [9]
B. Surgical management					
Endoscopic electrocautery for posterior epistaxis	2005	Prospective	43	Effective localization of source and control	Thornton, et al. [47]
TESPAL for control of refractory bleed	2003	Retrospective	127	98% control rate with no further therapy	Kumar, et al. [20]
TESPAL versus packing for recurrent epistaxis	2006	RCT	19	TESPAL superior for control, comfort, hospital stay and cost	Moshaver, et al. [28]
TESPAL +/− ant. ethmoid ligation for refractory bleeding	2000	Retrospective	287	TESPAL +/− ant. Ethmoid ligation equally effective as conventional measures, but improved cost and shorter stay	Srinivasan, et al. [17]
Embolization for refractory epistaxis	2008	Retrospective	70	Effective for control but increased cost	Christensen, et al. [48]
IMA ligation versus embolization for refractory posterior epistaxis	1998	Retrospective	39	IMA ligation more effective, but increased minor complications	Cullen, et al. [22]
Surgery versus packing versus embolization for posterior epistaxis	2002	Retrospective	203	Both surgery and embolization more effective for control; Surgery decreases hospital stay and cost	Klotz, et al. [26]

IMA, internal maxillary artery; TESPAL, transnasal endoscopic sphenopalatine artery ligation; RCT, Randomized Control Trial.

stay, transfusions, complications, or deaths between packing, embolization, and surgery, but the study did show a significant decrease in hospital charges in the packing group as compared to the embolization and surgery groups. However, Klotz et al. showed that early intervention with invasive measures results in a shorter hospital course, improved control of bleeding, decreased discomfort as associated with packing, and ultimately *less* cost [26,27]. In a randomized, prospective trial, Moshaver et al. further added support to early surgical intervention, demonstrating that health care costs were decreased by more than 50% and earlier hospital discharge was facilitated when posterior epistaxis was treated with temporizing packing followed by early TESPAL [28].

In the ICU setting in a patient population with multiple comorbidities, it is often the overall stability of the patient, ability to tolerate general anesthesia (for surgical intervention), or ability to tolerate angiography (e.g., no history of severe atherosclerosis, ability to lay flat, adequate renal functio) that dictates the most appropriate course of care for a patient with severe epistaxis. An in-depth knowledge of the treatment modalities available is critical to the clinician responsible for the direction of therapy (Table 146.2).

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CHAPTER 147 ■ ESOPHAGEAL PERFORATION AND ACUTE MEDIASTINITIS

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ESOPHAGEAL PERFORATION

Introduction

Esophageal perforation is both a highly lethal disease and primarily a surgical problem, and has remained such since nearly 4,000 BC as documented in the Edwin Smith Papyrus. Boerhaave then recorded his classical description of spontaneous rupture of the esophagus in 1724 [1]. Recently, there has been a shift in the etiology of esophageal perforation such that iatrogenic injury from instrumentation is the most common cause of esophageal perforation accounting for 40% of cases, while trauma represents 20%, spontaneous rupture (Boerhaave's) 15%, and tumor, foreign bodies, and operative injury collectively represent the remaining 25% of cases, leaving the two

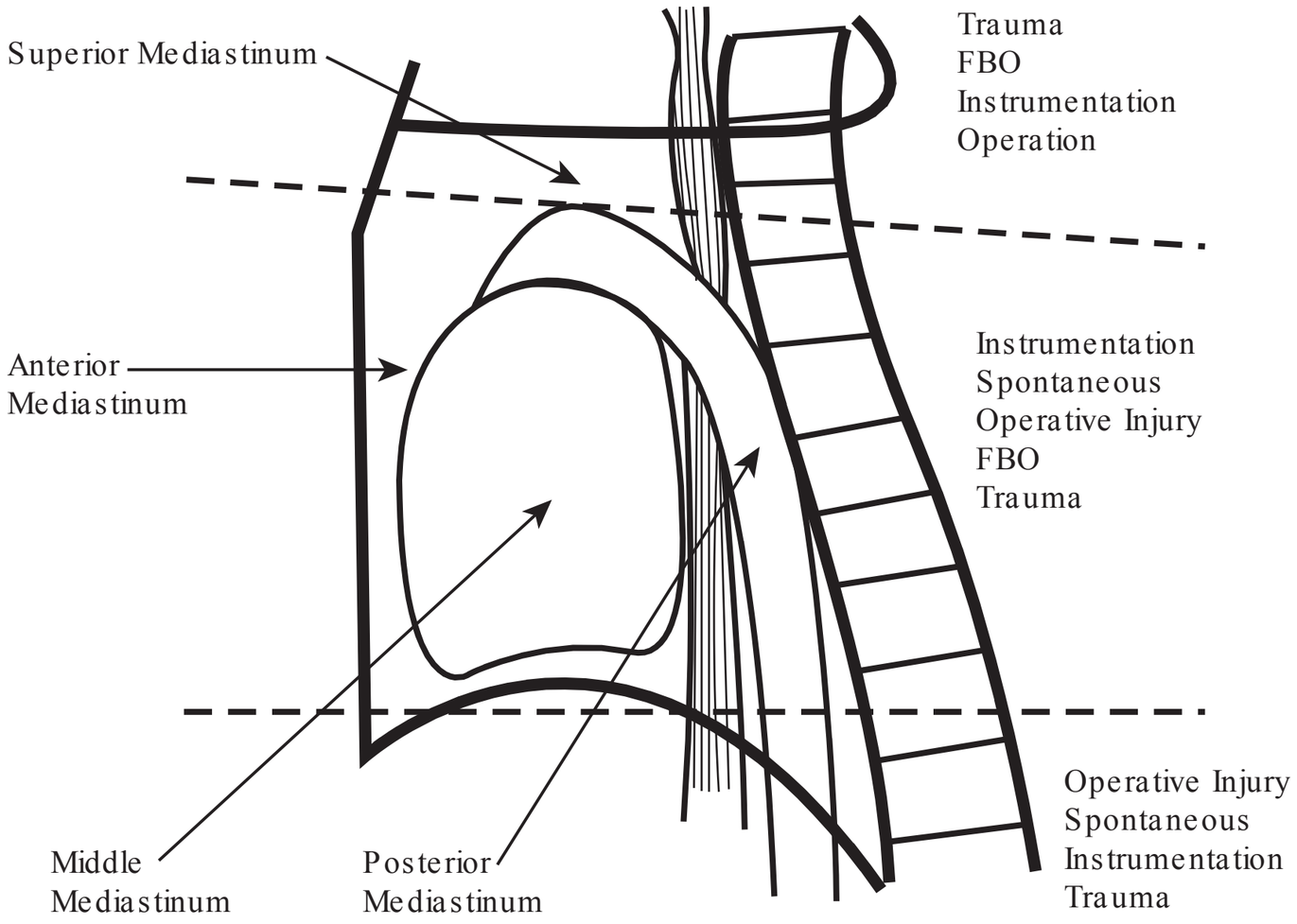

FIGURE 147.1. Zones of the mediastinum: these are identified on the left-hand side of the diagram. The superior mediastinum contains the thymic remnants, brachiocephalic veins, superior vena cava, aortic arch, trachea, phrenic nerve, vagus nerve, and the left recurrent laryngeal nerve. The anterior mediastinum contains primarily adipose and lymphatic tissue. The middle mediastinum is composed of the heart, pericardium, pulmonary trunk, aortic root, phrenic nerve, and tracheal bifurcation. The posterior mediastinum holds the descending thoracic aorta, azygos vein, esophagus, sympathetic chains, splanchnic nerves, and the thoracic duct. The right side of the diagram depicts each region of the esophagus, cervical, thoracic, and abdominal, and the injuries that occur there in decreasing order.

most common causes in the modern era as endoscopy related injury and anastomotic leakage [2]. The mortality associated with perforation of the esophagus remains high despite the most modern surgical and medical care, and ranges from 10% for early diagnosis to 75% for cases with late presentation.

Esophageal Anatomy

The esophagus is a muscular tube that extends from the pharynx to the stomach and is between 23 and 27 cm in length. It has three anatomic narrowings at the upper esophageal sphincter, at the level of the aortic arch and crossing of the left mainstem bronchus, and at the lower esophageal sphincter. The wall of the esophagus is comprised of the outer longitudinal muscle and the thicker inner layer of circular muscle. The innermost layer is the epithelial mucosa of the esophagus. The blood supply to the esophagus in the cervical region is primarily derived from the inferior thyroid artery. The thoracic esophagus receives its primary blood supply from the bronchial arteries and also receives branches directly from the descending thoracic aorta. The left gastric artery and the inferior phrenic arteries supply the abdominal portion of the esophagus. These arteries form a rich submucosal network of anastomoses that permit extensive mobilization and resection without fear of devascularization. The innervation of the esophagus is primarily from the vagus. Injury to the recurrent laryngeal branch of the vagus is well known for resulting in vocal cord paralysis, but less well known is the fact that significant functional impairment also occurs in the cricopharyngeal constrictor and motility of the cervical esophagus, contributing to the risk of aspiration after such an injury.

Pathophysiology

The most common locations for perforation of the esophagus to occur are at the narrowest portions of the organ but they can and do occur at any point. The absolute narrowest area in most people is at the cricopharyngeus muscle at the level of C5–C6, which corresponds to the upper esophageal sphincter (UES). This represents the portion of the esophagus most often injured during endoscopy and the risk is increased with hyperextension of the neck and in patients with bone spurs on the anterior surface of the vertebral bodies secondary to the presence of minimal tissue in the posterior cervical compartment between the posterior wall of the esophagus and the spine. The incidence of perforation during flexible endoscopy is about 0.03%; this is markedly improved over the era of routine rigid endoscopy which carried a much higher incidence of injury in the 0.11% range. Other iatrogenic causes of injury at the UES is transesophageal echocardiography performed during cardiac surgery and has a slightly higher incidence at 0.18% and other manipulations of the hypopharynx as in endotracheal intubation or nasogastric tube placement (Fig. 147.1).

The next narrow portion is at the level of the aortic arch and left mainstem bronchus and this is a common site for foreign body obstruction and ultimate perforation. Fish and chicken bones are the most common offenders in adults, while children tend to have a much wider variety of culprit objects such as safety pins, parts of toys, plastic elements. In the elderly, oral hardware such as dentures account for the majority of ingested items.

The gastroesophageal junction (GEJ) is the third region of narrowing and is most often perforated iatrogenically during dilations of the distal esophagus for achalasia or distal esophageal strictures. Perforation also results from biopsies in this area during evaluations for metaplasia. The GEJ is the most severely injured area of the esophagus in patients with accidental or intentional ingestion of chemical substances. The relaxation of the LES in response to injury along with intense pylorospasm results in continued reflux of caustic substances into the distal esophagus. This prolongs contact with the mucosa resulting in more severe injuries. Alkaline substances tend to create a more severe injury to the esophagus due to the liquefactive necrosis and the slow transit time, while acids tend to move more quickly through the esophagus and create a coagulative necrosis limiting the depth of injury.

Spontaneous perforation of the esophagus (Boerhaave's) is most commonly discovered in the distal left posterior lateral aspect about 2 to 3 cm from the GEJ. This area has a less developed muscular layer to accommodate the exit of neurovascular structures and tapering of the muscle as to spread out onto the stomach wall, allowing the increased pressure during retching to result in rupture into the left chest. The cervical esophagus is much more vulnerable to external trauma than

TABLE 147.1

CAUSES OF ESOPHAGEAL PERFORATION

Spontaneous (Boerhaave's syndrome)
Iatrogenic
Endoscopy (esp. with sclerotherapy or biopsy)
Dilation with bougie or balloon
Naso/orogastric tubes
Endotracheal intubation
Operative injury
Trauma
Caustic ingestion
Infections (tuberculosis, herpes simplex, CMV)
Malignancy
Zollinger–Ellison syndrome

Note: The percentages of each etiologies will vary depending on the location of the perforation and time period studied.
CMV, cytomegalovirus.

the thoracic esophagus and up to 6% of penetrating injuries to the neck may have a concomitant esophageal perforation, whereas only 0.7% of penetrating thoracic injuries result in an injury to the esophagus. Blunt traumatic injury to the esophagus is extremely rare and is almost always located in the cervical esophagus (Table 147.1).

Presentation

Delay in diagnosing an injury to the esophagus is the most important determinant of mortality in this disease and thus a high index of suspicion should be maintained whenever injury to the esophagus is a possibility in a differential diagnosis. Perforation of the esophagus leads to contamination of the surrounding tissues in the neck, mediastinum, or abdomen and localized sepsis due to the degree of aerobic and anaerobic bacterial contamination. Chief complaints are therefore related to the effects of local tissue inflammation and the systemic inflammatory response. The most common presenting symptom in patients with esophageal perforation is pain followed by other common signs including fever, dyspnea, and subcutaneous emphysema, which may extend into the head and neck. Auscultation of the heart tones may reveal a crunching sound that is related to air in the mediastinum and is a classic sign of esophageal perforation. Pain resulting from esophageal perforation is dependent on the location. A cervical perforation tends to cause less pain and more vague symptoms of neck stiffness, headache, and backache. Symptoms with more distal perforation in the thoracic esophagus tend to be substernal and can lateralize to the side of perforation with proximal esophageal perforations tending to be on the right side and more distal perforations on the left side. This must be differentiated from acute coronary syndromes and should be considered in patients with severe chest pain after an acute myocardial infarction has been eliminated as the etiology.

Presenting signs of perforation may be subtle and nonspecific in the early phase with tachycardia being the most well recognized, and persistent tachycardia in a patient who has undergone an endoscopic evaluation or a surgical procedure involving the esophagus should warrant an evaluation for rupture. As the course progresses, these patients rapidly develop systemic sepsis with hypotension and tachycardia, tachypnea and worsening respiratory distress, renal failure, and mental status alterations. Failure to recognize septic shock and intervene early in this patient population may lead to death within 12 to 24 hours.

Diagnostic Evaluation

A chest radiograph is often one of the first tests obtained in patients with pain in the chest or neck. The presence of a pleural effusion, pneumothorax, or pneumomediastinum, in the setting of a suspicious history, is highly suggestive of an esophageal perforation. A contrast esophagram, however, is the gold standard for diagnosis of perforation. It has a high sensitivity and specificity and is relatively easy to obtain in any facility. Following an initial evaluation with water-soluble contrast, a barium contrast study should be done to rule out a leak. The false negative rate for esophageal perforation utilizing water-soluble contrast is 20% to 25%, even when digital subtraction imaging techniques are used [3,4]. Therefore, a negative study with water-soluble contrast does not complete the evaluation [5]. Concern over the inflammatory reaction associated with barium extravasation in the setting of bacterial contamination is warranted if an intra-abdominal perforation is suspected and the patient is presenting with peritonitis [6]. Such a response has not been demonstrated in the mediastinum and barium should be used to increase the sensitivity of the imaging [7]. Patients who cannot perform a swallowing test or are in extremis are most often imaged with computed tomography with oral contrast administered by nasogastric tube, which must be positioned in the proximal esophagus to provide diagnostic value. The key finding on a computed tomography (CT) scan for diagnosing a perforation is an extraluminal collection of gas or subcutaneous emphysema. Periesophageal fluid collections with air-fluid interfaces, esophageal wall thickening effacement of fat planes, extravasation of oral contrast and pleural effusions are other radiographic findings consistent with a perforation. Computed tomography is also useful in the evaluation for abscess or empyema formation with a long-standing leak [8–11] (Fig. 147.2).

The role of esophagoscopy in the diagnosis of esophageal perforation has been established in the setting of traumatic injuries with a high sensitivity for detecting injury [12–14]. In non-traumatic settings, the sensitivity has not been established and the use of endoscopy remains as an adjunct to imaging modalities. This may be related to the difficulty in locating sites of perforation in the esophageal mucosa when there are no attendant signs of trauma [15].

Treatment

There is a paucity of reliable data regarding the treatment of esophageal perforation. This is partly a result of the fact that patients present with a wide variety of symptoms, differing severity of injury and are treated by several different specialties. Several principles in the management of esophageal perforation are paramount: control of ongoing soilage by closure of the leak, management of sepsis with adequate drainage and support of the patient with fluids, nutrition, and appropriate antibiotics.

After goal-directed resuscitation and initiation of broad-spectrum antibiotic therapy, the treatment of choice for most patients with perforations of the esophagus remains surgical. For early perforations less than 24 hours in hemodynamically stable patients, consideration may be given to direct primary repair of the injury. This is generally possible in cases where there is a small injury with little soilage or devitalized tissue in a surgically accessible location and early detection has been achieved. Access to the cervical esophagus is generally obtained through an anterior neck incision along the anterior border of the left sternocleidomastoid muscle. The carotid sheath and its contents are retracted laterally and the thyroid and trachea retracted medially to expose the esophagus. In the mediastinum,

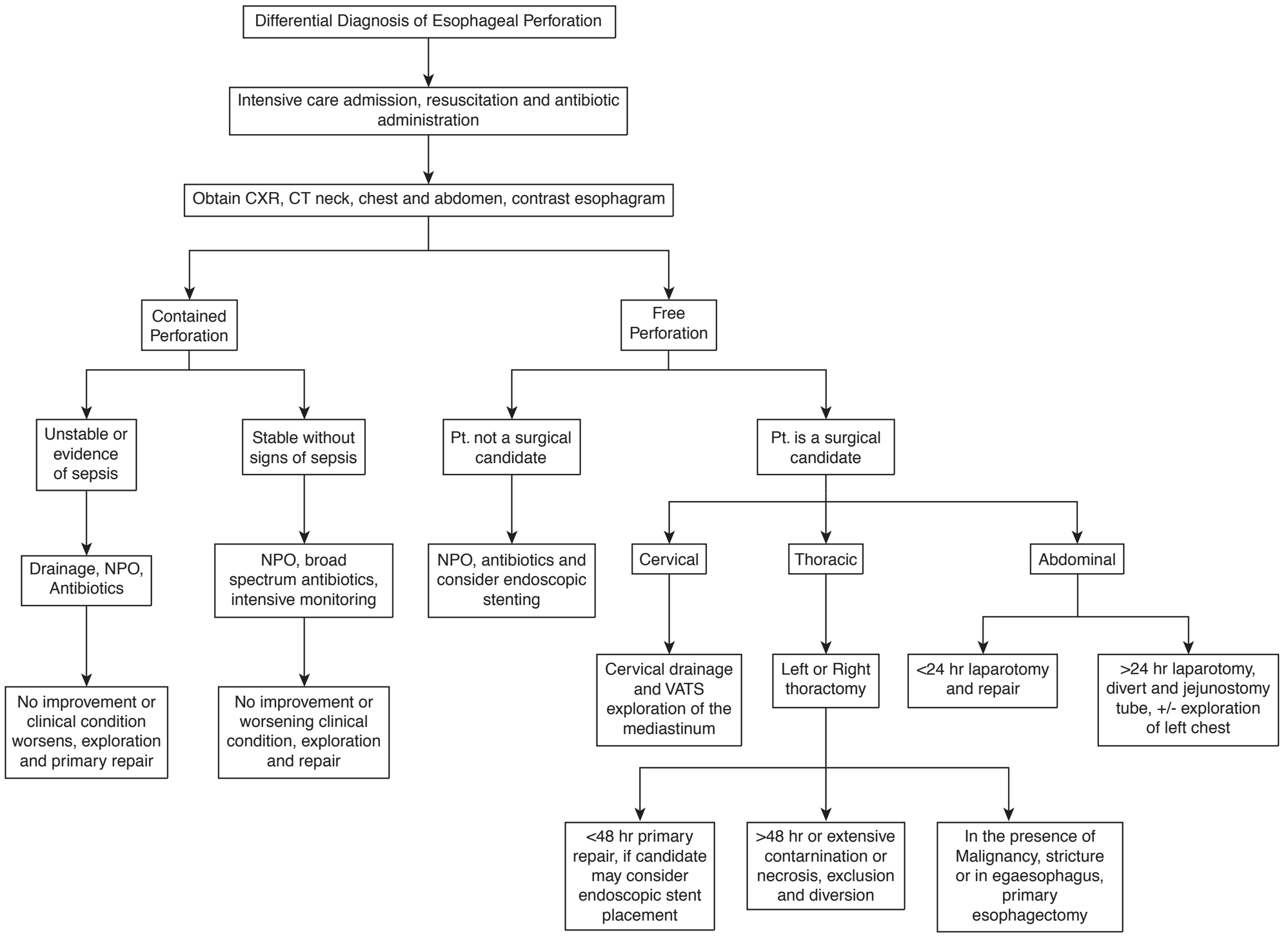

FIGURE 147.2. Algorithm for the diagnosis and management of a perforation of the esophagus. Early diagnosis followed by resuscitation and surgical consultation are the keys to decreasing the mortality from this highly lethal condition.

a right posterolateral thoracotomy is used to access lesions in the middle third of the esophagus and a left posterolateral thoracotomy provides exposure for the distal third of the thoracic esophagus. Upper midline laparotomy or left thoracotomy may be used to access the gastroesophageal junction. If amenable to repair, the esophagus is usually closed with a single layer of interrupted full thickness sutures and the anastomosis is reinforced with a well-vascularized local tissue flap from the latissimus dorsi muscle, pericardium, or omentum.

In cases where the diagnosis has been delayed for more than 24 hours, there is extensive tissue injury, or intense local sepsis, primary repair is ill-advised. In this situation, it is prudent to perform a resection of the esophagus or proximal diversion with a cervical esophagostomy and exclusion of the injured esophagus with creation of enteral feeding access. After the resolution of sepsis and once the patient is nutritionally repleted, reestablishment of intestinal continuity can be achieved with a gastric pull-up or intestinal interposition techniques. If there is a coexisting underlying esophageal pathology such as megaesophagus, achalasia, esophageal stricture, or carcinoma, esophagectomy with or without reconstruction is the operation of choice. In patients who cannot tolerate a definitive repair, surgical management should be limited to placement of an esophageal T-tube for drainage and creation of a controlled esophageal fistula.

Patients who have a small contained perforation, stable vital signs and no ongoing sepsis may be candidates for nonoperative management. This includes radiographic demonstration that ongoing soilage is absent and drainage of intrathoracic fluid collections is amenable to interventional radiology or by the placement of thoracostomy tubes. These patients should also be placed on a substantial course of culture directed antibiotic therapy, and be started on parenteral nutrition with complete rest of the upper gastrointestinal tract.

Given the high mortality associated with surgical repair of esophageal perforations, it is not surprising that innovation continues in this complex disease process. The development of even more advanced endoscopic therapeutic modalities has provided some new options in the management of these patients, including endoscopic closure and stenting. There are several small series which have been published recently that suggest that endoscopic stenting of spontaneous or iatrogenic esophageal perforations can be effective as initial or definitive therapy [16]. There is experimental evidence demonstrating the efficacy of endoluminal closure devices for management of esophageal perforation. There appears to be a faster rate of healing and return to normal function with the use of clipping devices over endoluminal suturing techniques [17]. Clinical evidence is limited to case reports and series, but does appear feasible. Although there is a clear selection bias favoring patients with less severe disease and more favorable prognosis, it is appealing to consider a therapy with a much less invasive approach and potentially less severe dysregulation of systemic inflammation. The other major endoluminal therapy in use is the esophageal stent. Endoscopically placed occlusive stents have been used to close perforations and quickly restore

intestinal continuity with good effect. A recent series reported that 23 patients were treated with endoluminal stents and they had no resultant mortality and only 10% went on to require surgical intervention [16]. This may represent a new paradigm in the management of this disease process that will have a less profound effect on the counter regulatory cytokine response and immune function.

Follow-up

In addition to the operative mortality, there is a high risk of anastomotic complications after repair of esophageal perforations approaching 40% to 50%. This includes stricture and disruption of the esophageal anastomosis [18]. In the immediate postoperative period, these patients should remain in the intensive care setting or in a specialized surgical unit where early signs of anastomotic complications can be identified and addressed in a timely fashion. Thoracostomy tubes are generally left in place until the first feeding to identify an early anastomotic dehiscence. Once the patient is discharged from the hospital, the most important chronic problem is stricture of the anastomosis and complaints of dysphagia should prompt a contrast imaging study of the esophagus.

MEDIASTINITIS

Introduction

Since the time of Boerhaave, physicians have recognized mediastinitis as a highly lethal disease for which treatments have only been developed in the very recent past [1]. The incidence of mediastinitis after coronary artery bypass grafting (CABG) ranges from 0.5% to 1.25% and carries an in-hospital mortality up to 14% compared to 1.1% in CABG patients who do not develop sternal wound infections [19,20]. Mediastinitis is also associated with a significant increase in long-term mortality after coronary artery bypass grafting with patients survival at 1 year dropping from 95% to 78% [19]. We now recognize a number of causes of mediastinitis in addition to the original description of spontaneous esophageal rupture. These include the acute causes of mediastinitis, iatrogenic perforation of the esophagus, post-sternotomy, head and neck infections, pulmonary infection, abdominal infections, chest wall osteomyelitis, or direct posttraumatic. Chronic causes of mediastinitis include granulomatous diseases, fibrotic diseases, autoimmune diseases, and drug reactions [21].

The mediastinum is divided into the superior and inferior regions, and the inferior mediastinum includes the anterior, middle, and posterior compartments [22]. The superior mediastinum is bounded by the pleura laterally, the thoracic inlet superiorly and inferiorly by a line extending from the sternal angle to the intervertebral disc between the fourth and fifth thoracic vertebral bodies. Structures contained in the superior mediastinum include the thymic remnants, brachiocephalic vein, superior vena cava, aortic arch and the branch vessels, the trachea and the phrenic, vagus and recurrent laryngeal nerves. The anterior mediastinum is defined by the posterior surface of the sternum and the anterior pericardium, the inferior margin of the superior mediastinum and the diaphragm. The anterior mediastinum is devoid of major anatomical structures and is primarily occupied by adipose, connective, and lymphatic tissue. The middle mediastinum consists of the heart and pericardium, the pulmonary trunk, phrenic nerves, and the distal trachea including the bifurcation into the right and left mainstem bronchi. The posterior mediastinum extends from the posterior surface of the pericardium to the spinal column. The major contents of this compartment are the descending aorta, azygos vein, esophagus, sympathetic chains, splanchnic nerves, thoracic duct, and lymphatics.

Acute Mediastinitis

The most common cause of acute mediastinitis is post sternotomy. The Centers for Disease Control and Prevention define mediastinitis as a deep sternal incisional surgical site infection [23]. The incidence of mediastinitis after sternotomy ranges from 0.4% to 5.0% in the literature with most series reporting 1% to 2%, and an associated mortality of 10% to 20% [19,24]. Risk factors associated with the development of a deep sternal wound infection can be divided into preoperative, intraoperative, and postoperative risks. Preoperative factors are male gender, presence of hypertension, chronic obstructive pulmonary disease, diabetes, obesity, large breast size, history of smoking, and older than 70 years [20,25–31]. Intraoperative variables include an extended cardiopulmonary bypass pump time, the use of autotransfused shed mediastinal blood, and harvest of both internal mammary arteries [32–34]. Postoperative risk factors include reexploration for bleeding, prolonged intubation, and tracheostomy [35–37]. Recognition of the importance of these predictors allows the intensivist to maintain a high index of suspicion in the immediate postoperative period for the development of this devastating complication (Table 147.2).

The next most common cause of acute mediastinitis is descending cervical infection generally from odontologic procedures or disease, tonsillitis, or pharyngitis. Infections of the head and neck region can reach the mediastinum by three primary pathways from the cervical fascial planes. The pretracheal, perivascular, and retropharyngeal spaces have all been implicated as routes for spread of descending infections to gain access through the thoracic inlet into the mediastinum [38]. Based on the report by Pearse in 1938, the retropharyngeal space was once thought to be the culprit in the majority (70%) of descending cervical infections, however, a small recent study suggests that the perivascular space may be more important and that the carotid sheath may need to be opened and drained in a majority of cases [39,40].

Presentation

Acute mediastinitis usually presents within the first 7 to 10 days after surgery with fever, leukocytosis, chest pain, dysphagia, or respiratory distress [41]. Other presenting symptoms

TABLE 147.2

RISK FACTORS FOR POSTOPERATIVE MEDIASTINITIS

Diabetes
COPD
Harvest of bilateral internal thoracic arteries
Tobacco use
Prolonged ventilation
Obesity
Advanced age
Renal failure
Prolonged bypass pump time
Extensive use of electrocautery
Bleeding requiring reexploration

COPD, chronic obstructive pulmonary disease.

include drainage or erythema in the sternal wound, presence of a sternal click or dehiscence of the sternum, and subcutaneous emphysema.

When the source of infection is the neck, the primary symptoms are neck and/or throat pain in the early phases followed by edema, dysphagia, and odynophagia which is generally easily recognized. Although fever and leukocytosis are relatively nonspecific findings, in the presence of chest pain in the postoperative period it should raise the suspicion for diagnosis. One must be alert to the possibility of acute airway obstruction in the case of descending infection secondary to airway edema or epiglottitis [42].

Diagnosis

The initial evaluation, especially in cases with respiratory compromise, usually includes a chest radiograph, which is often nondiagnostic, but may show alterations in the normal tissue planes with edema, fluid, or air [42]. Chest x-ray may demonstrate diffuse mediastinal widening or air-fluid interfaces in the mediastinum in advanced cases. With esophageal perforation pneumothorax, pneumomediastinum and pleural effusion are common findings.

Computed tomography imaging of the chest with both oral and intravenous contrast is generally the next study evaluating pathologic processes in the thorax and has the most utility in identifying major infections in the mediastinum. CT allows the easy evaluation of both the neck and the abdomen to assess the relationship of any fluid collections in the chest to other potential sources of infection. It also allows precise localization of the fluid collection and possible intervention in selected cases. CT is also an important element in the preoperative planning of surgical drainage procedures and should not be omitted in the work up of this highly lethal disease. In cases where esophageal perforation is suspected, a contrast esophagram with Gastrografin is indicated as discussed in the previous section.

The diagnosis of mediastinitis is defined by the Centers for Disease Control as an infection in a patient who has one of the following conditions: (i) organisms cultured from mediastinal tissue or fluid, obtained during a surgical operation or needle aspiration; (ii) evidence of mediastinitis seen during a surgical operation or histologic examination; (iii) a patient with fever, chest pain, or sternal instability with no cause and at least one of the following: (a) purulent discharge from mediastinal area, (b) organisms cultured from blood or discharge from mediastinal area, or (c) mediastinal widening on chest x-ray [43].

Treatment

The treatment of mediastinitis is directed toward the primary pathological process, but initial measures include the administration of broad-spectrum antibiotic therapy, fluid resuscitation, and surgical drainage for control of the source. Mediastinitis tends to be a polymicrobial infection, however, antimicrobial therapy can be directed toward likely organisms depending on the etiology of the infection. Cultures from patients with descending cervical mediastinitis secondary to an odontologic or oropharyngeal process are likely to grow Gram-negative aerobes and anaerobes, including anaerobic *Streptococcus* and *Bacteroides* species. Deep sternal wound infections in postoperative mediastinitis most often grow *Staphylococcus aureus*, aerobic *Streptococcus*, *Pseudomonas aeruginosa*, and *Enterococcus* spp. When the origin of the septic focus is within the chest wall, periosteum of the ribs, or pleural space, the infected tissues may harbor tuberculosis or fungi.

Patients with mediastinitis will often present late in the course of the disease due to the nonspecific and misleading nature of the early symptoms. Because of this they often have clinical signs of sepsis with significant third space fluid losses and vasodilatory shock. Volume resuscitation should be started early with emphasis on goal-directed resuscitation to restore hemodynamic parameters. Most of these patients will ultimately require surgical intervention and adequate cardiac preload is essential for successful anesthesia induction. Once volume expansion is adequate, consideration can be given to the addition of vasoactive agents to increase the systolic blood pressure if vasodilation is an element of the patient's presentation.

Surgical drainage is the standard definitive therapy in all forms of mediastinitis. Descending cervical infections will require the primary oral process to be addressed in addition to incision and drainage of the neck through either a vertical incision along the anterior border of the sternocleidomastoid muscle, and thoracotomy or thoracoscopy for mediastinal drainage and placement of thoracostomy tubes for continued chest drainage. Incisions in the neck should be allowed to heal by the secondary intention to prevent ongoing sources of infection. Occasionally, infections limited to the superior mediastinum may be adequately addressed by the cervical incision, however, these patients must be carefully selected to avoid leaving the patient with ongoing septic foci as nearly 50% of patients treated by the cervical approach alone go on to require thoracotomy for unrecognized mediastinal disease [44].

Poststernotomy mediastinitis requires an aggressive approach to reduce the morbidity and mortality associated with this complication. Exploration of the mediastinum by reopening the median sternotomy incision is the standard approach. All necrotic tissue and bone are widely debrided, and tissue is mobilized as a flap to fill the dead space left by the debridement. Reclosure of the sternum by direct rewiring has been reported to carry a mortality up to 45%, which is unacceptably high [45]. Tissue flaps may be created with various rotational techniques or omental harvest, but the most common is medialization of bilateral pectoralis major muscles as local flaps. Using omentum has the disadvantage of requiring a laparotomy and opening of an additional body cavity, but has the distinct advantage of being simple and performed quickly in the unstable patient. Vacuum closure of the mediastinum is gaining acceptance as an alternative to immediate flap closure. Reports indicate that mortality is comparable when used as definitive therapy or as a bridge to a delayed myocutaneous flap closure [46].

Chronic Mediastinitis

Granulomatous infections like histoplasmosis, syphilis, tuberculosis, and coccidiomycosis as well as noninfectious processes like sarcoidosis cause a subacute prolonged mediastinal inflammation called chronic mediastinitis. The primary pathologic process is one of diffuse fibrosis of the mediastinum. This may also result from prolonged acute mediastinitis. Risk factors for development of chronic mediastinitis include the presence of autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, and Raynaud's phenomenon, or the presence of mediastinal foreign bodies. Symptoms are generally low grade and well tolerated in the early stages and include cough, dyspnea, wheezing, chest pain, or dysphagia. Compression or obstruction of major vascular structures such as the superior vena cava (SVC) may lead to SVC syndrome. Radiographic studies may demonstrate widening of the mediastinum resulting from diffuse fibrosis or calcifications of involved lymph nodes and granulomas. Contrast CT of the chest is particularly helpful in the evaluation of vascular compression but will also clarify the extent of the mediastinal involvement in the fibrotic process and evaluate the lung parenchyma and associated thoracic viscera. There is no single accepted or effective treatment for chronic mediastinitis. Antibiotics are indicated for documented

bacterial or fungal infection, while chemotherapeutic regimens have had limited success in modulating the ongoing inflammatory process, and surgical therapy is generally limited to tissue biopsy for diagnosis. For vascular compression, endovascular stenting may have an increasing role in palliation of SVC syndrome.

Esophageal perforation and mediastinitis represent relatively rare disease processes that often present as acute life threatening illnesses. As such they are not particularly amenable to well designed randomized controlled trials in the evaluation of different therapeutic options. A review of the literature does not demonstrate any class I data related to therapies for the treatment of these diseases and such data is not likely to be forthcoming. Further advances are likely to continue to come from retrospective analysis of innovative approaches to these complex problems.

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CHAPTER 148 ■ MANAGEMENT OF THE POSTOPERATIVE CARDIAC SURGICAL PATIENT

SAJID SHAHUL, CATHY DUDICK AND ALAN LISBON

The management of the postoperative cardiac surgical patient is a dynamic process that requires modern intensive care unit (ICU) technology and sharp clinical skills. Early detection of acute complications has a significant impact on morbidity and mortality. The postoperative care of cardiac surgical patients is best handled using a systematic approach [1,2].

MONITORING

The restoration and maintenance of physiologic homeostasis without further injury to the heart and other organs represent the most important goal in the care of the postoperative cardiac surgical patient and requires proper patient monitoring. An arterial cannula, usually in the radial artery, permits easy access to blood for various laboratory tests (see Chapter 3) and provides the ability to measure systemic blood pressure continuously, mean arterial pressure (MAP) being the value of most interest. The MAP is the least dependent on site or technique of measurement and the least affected by measurement damping; it also determines tissue blood flow by autoregulation [3].

At least one lead of the surface electrocardiogram also should be displayed, with several leads being monitored for ST-segment changes. Pulse oximetry allows assessment of oxygen saturation and reduces the need for arterial blood gases.

A triple-lumen pulmonary artery catheter (PAC) inserted through an internal jugular vein permits measurement of the right atrial, pulmonary artery, and pulmonary artery occlusion (PAOP) pressures and the determination of cardiac output (CO) and mixed venous saturation. Pulmonary artery catheters with an oximeter probe at the distal end allow continuous monitoring of mixed venous oxygen saturation and cardiac index. However, based on multiple, randomized controlled clinical trials in a variety of settings, the routine use of pulmonary artery catheterization does not lead to improved clinical outcomes [4–9]. Although the PAC-Man trial, an open randomized trial involving 65 UK ICUs and over 1,000 patients, demonstrated no clear benefit or harm in using a PAC [4], the use of a PAC carries attendant risks such as infection, pulmonary artery rupture, and arrhythmia.

Transesophageal echocardiography is now used both as a monitoring and a diagnostic tool, both in the operating room and the ICU. It allows real-time evaluation of intracardiac blood flow, anatomy, and function. It may be superior to invasive monitoring [10], particularly in the setting of valvular disease or respiratory disease when pressure-based readings may not accurately reflect volume status. In both cardiac and noncardiac patient populations, several studies demonstrated that TEE provided unexpected information that significantly altered the therapeutic plan, even in patients with an indwelling PAC [10]. The therapeutic management decisions gleaned from TEE ranges from 10% to 69%, with the majority of studies demonstrating the 60% to 65% range. The diagnostic yield of TEE approaches 78% [11].

INITIAL ASSESSMENT

A brief but systematic physical examination of the patient is mandatory on arrival in the ICU. Inspection of the skin and extremities may reveal intraoperative injuries, infiltration or disconnection of intravenous (IV) infusions, absence of pulses, signs of drug or transfusion reactions, or evidence of hypoperfusion. Auscultation of the chest may reveal unilateral absence of breath sounds due to malposition of the endotracheal tube or pneumothorax. The abdomen should be inspected to ensure that no abdominal distention is present. Mediastinal and chest tubes should be examined for drainage.

Initial laboratory studies should include arterial blood gas, hematocrit, sodium, potassium, glucose, calcium, magnesium, prothrombin time (PT), partial thromboplastin time (PTT), and platelet count. A portable chest radiograph and a 12-lead electrocardiogram with atrial electrograms should be obtained immediately on admission to the ICU. The postoperative chest radiograph should be inspected with specific attention to the following: (a) pneumothorax and mediastinal shift; (b) position of the endotracheal tube, nasogastric tube, and intravascular catheters; (c) size and contour of the mediastinal silhouette; and (d) pleural and extrapleural fluid collections.

PHYSIOLOGIC PRINCIPLES OF CARDIAC FUNCTION

Cardiac function is determined by intrinsic myocardial properties as well as by ambient loading conditions. The inotropic state (contractility) of the myocardium during systole is a determinant of systolic stroke volume (SV). Systolic function is also determined by ambient hemodynamic conditions (heart rate [HR], preload, and afterload). The conceptual framework that provides maximal information about intrinsic myocardial properties, as well as the interrelationships between systolic contractility, preload, and afterload, is represented by the ventricular pressure–volume (PV) relationship (Fig. 148.1). The cardiac cycle has four phases: (a) passive ventricular filling during diastole (which, in Fig. 148.1, has been extended as a curvilinear line to describe the distensibility of the ventricle beyond the range of the illustrated cardiac cycle), (b) isovolemic systole (before aortic valve opening), (c) systolic ejection, and (d) isovolemic relaxation.

The SV for an individual cardiac cycle can be obtained by subtracting end-systolic ventricular volume from the end-diastole volume (EDV). The systolic ejection fraction can be determined from the fractional relationship between SV and EDV. This framework aids in conceptualizing and predicting the effects of changes in loading conditions and contractility on measurable hemodynamic parameters.

Left atrial pressure can be measured, or its mean can be estimated by the measurement of PAOP pressure or pulmonary diastolic pressure. These three pressures are equal only under

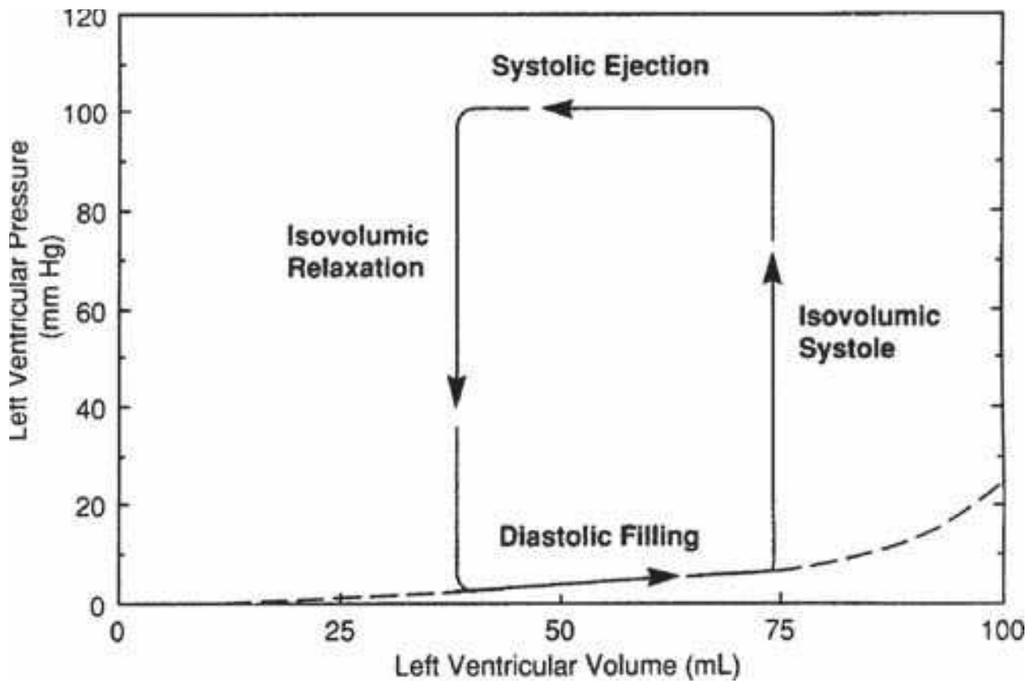

FIGURE 148.1. The left ventricular pressure-volume diagram. Phases of the cardiac cycle.

ideal circumstances. Generally, pulmonary diastolic pressure exceeds pulmonary artery occlusion pressure, which exceeds mean left atrial pressure. These differences are determined by gravitational effects related to pulmonary artery catheter position and by diastolic pressure gradients in the pulmonary vasculature.

Although the systolic SV of the left ventricle is not measured directly, it can be determined from measurements of CO and HR. If LV systolic ejection fraction (EF) has been determined, the end-diastolic volume (EDV) and end-systolic volume (ESV) of the left ventricle can be determined: EDV = SV/EF and ESV = EDV − SV.

Preload is an estimation of average end-diastolic myocardial fiber length and correlates best with ventricular EDV. As the left ventricle distends, EDV, rather than end-diastolic pressure, is a highly predictive determinant of systolic function. Mechanical interaction between the two ventricles and between each ventricle and the surrounding mediastinal and thoracic structures can also influence ventricular distensibility. LV end-diastolic pressure (rather than EDV) can be used to monitor preload only when those factors that alter ventricular distensibility are constant. When ventricular distensibility is changing (due to, for example, the loss of myocardial compliance that occurs with transient ischemia), the measurements or estimates of ventricular diastolic pressure do not accurately represent preload.

The term *afterload* usually is used to describe the forces that retard the ventricular ejection of blood. The afterload of the right and left ventricles is determined primarily by the resistive and capacitive characteristics of the pulmonary and systemic circulations. As blood is ejected from the ventricle, the actual afterload forces that oppose the shortening of myocardial fibers are distributed as stresses throughout the ventricular walls.

The Frank-Starling principle is useful in predicting the hemodynamic outcome of therapeutic interventions. This is illustrated by the curvilinear relationship between ventricular stroke work (*y*-axis) and ventricular end-diastolic pressure (*x*-axis). When preload is represented by EDV, rather than by end-diastolic pressure, this relationship becomes linear and is minimally affected by afterload and HR [12]. The slope of this relationship is a sensitive indicator of intrinsic myocardial performance and responds appropriately to inotropic interventions. The augmentation of stroke work by increases in preload is referred to as *preload recruitable stroke work* (Fig. 148.2).

Increases in CO, afterload, preload, inotropic state, and HR are all achieved with increased myocardial oxygen demand. Intraoperatively, myocardial oxygen demand is eliminated by hypothermia and chemical cardioplegia. Postoperatively, if the myocardial work is too intense or the blood supply is too small, myocardial ischemia, failure, and infarction may result. An important feature of myocardial oxygen consumption is that oxygen extraction is nearly maximal at rest, so that increases in myocardial oxygen consumption can only be achieved by increases in coronary blood flow. Increased afterload is, to a degree, self-compensatory in that increased diastolic coronary perfusion pressure tends to increase coronary blood flow. Increases in inotropic activity may also be associated with increases in myocardial blood flow and a correspondent increase in diastolic aortic pressure.

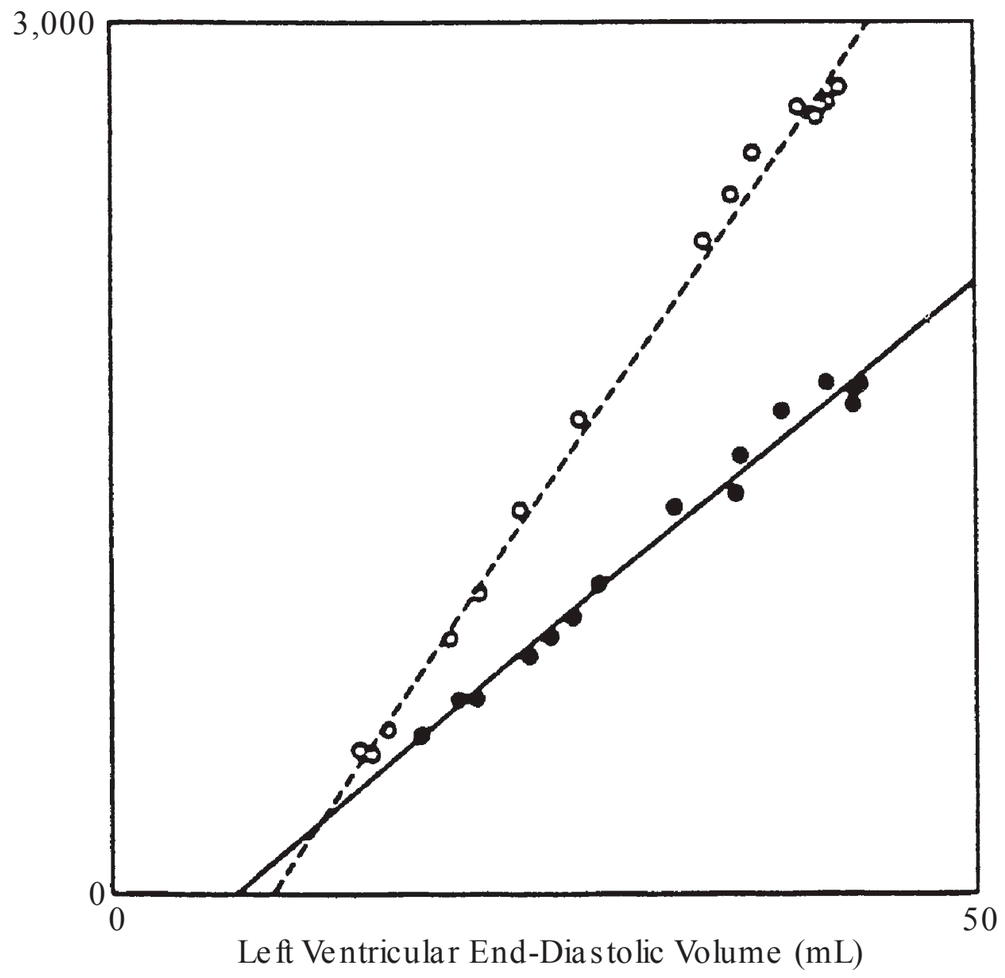

FIGURE 148.2. The preload recruitable stroke work relationship for the left ventricle. The slope of this relationship is sensitive to inotropic interventions and is increased by the infusion of calcium. [Reprinted from Glower DD, Spratt JA, Snow ND, et al: Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation* 71:994, 1985, with permission.]

Maximizing cardiac function to meet metabolic demands, therefore, involves the manipulation of volumes and pressures that affect preload and afterload and the support and enhancement of myocardial contractility. Andre and DelRossi [13] note that the postoperative myocardium is cold and stiff and generally behaves as a pressure-overloaded system. Volume may be needed despite high measured filling pressures. As the patient recovers and the myocardium warms, compliance improves and the relationship of filling pressures to ventricular volumes changes.

Initial Status

On arrival to the ICU, a systematic assessment should include preoperative history with attention to medications and cardiac function, intraoperative history, vital signs, and physical examination. Immediate goals and short-term goals need to be established. Many patients arrive hypothermic with temperatures ranging from 34°C to 36°C as a result of deliberate systemic cooling during cardiopulmonary bypass. Persistent peripheral vasoconstriction can be the result of elevated angiotensin levels [14]. Shivering during rewarming increases metabolic and circulatory demands, increases carbon dioxide production, and complicates ventilator management. Shivering can be eliminated with paralyzing agents and sedation [15,16]. The patient is generally maximally warm by 4 to 6 hours after operation.

As the patient rewarms and awakens, the goal is to support the recovering myocardium until it is independently able

to meet metabolic demands. Cardiac output is measured and normalized to cardiac index (CI) by dividing it by the patient's body surface area. Efforts to correct an initial cardiac index of less than 2 L per m^2 per minute should be made because low cardiac index is associated with an increased risk of death [17,18]. The clinical correlates of reduced cardiac index are pale and cool skin, cyanotic mottling of the skin (occurring first over the knees), decreased urine output, and deterioration of mental status or slowness in awakening from anesthesia. A low CI and decreased peripheral perfusion also cause metabolic acidosis (from lactic acid accumulation in poorly perfused tissues; see Chapter 71), which, to a mild degree, occurs even after routine operations.

Normally, the mixed venous hemoglobin saturation (SvO_2) should be 60% or higher. If it is less than 50%, a high likelihood of death exists [17,19]. The SvO_2 should be interpreted in light of the cardiac index and hemoglobin. In the worst situation, and the one that often leads to death, the SvO_2 may be adequate only because so much of the peripheral tissues are underperfused [17]. In this case, however, the cardiac index also is reduced. The value of SvO_2 is limited because it does not describe the balance of oxygen in those tissues with fixed oxygen extraction. The kidney, skin, and resting muscle can maintain viability during reduced blood flow by augmenting oxygen extraction. The heart and brain, on the other hand, extract oxygen nearly maximally at rest, and their vulnerability to ischemia is not reflected by widened oxygen extraction.

Postoperative hypertension is common and may be a consequence of several factors, such as inadequate sedation, hypoxemia, hypercarbia, activation of cardiogenic reflexes, vasoactive drug administration, and withdrawal of beta-blocking agents; however, intense vasoconstriction accounts for most of the hypertension. Failure to control the blood pressure increases the risk of aortic tear, elevates myocardial oxygen demand, leading to the possibility of decreased subendocardial perfusion and ischemia.

As a consequence of fluid administration, the patient seen in the ICU just after an operation on cardiopulmonary bypass usually weighs 2 to 5 kg more than preoperatively. Urine output is typically high in patients with good LV function. If urine output is low, intravascular volume or CO may be low. Inappropriate antidiuretic hormone excretion commonly exists as a consequence of operative trauma. The patient is frequently treated with IV nitroglycerin and other afterload-reducing and venodilating agents. These agents shift blood volume to the periphery and consequently decrease preload. These factors tend to reduce urine output.

TABLE 148.1

CAUSES OF LOW CARDIAC OUTPUT

- Inadequate preload
  - Volume deficit
  - Excessive positive end-expiratory pressure
- Increased afterload
  - Vasoconstriction from endogenous catecholamines (sympathetic stimulation)
    - Painful stimuli
    - Nonpulsatile flow during cardiopulmonary bypass
    - Hypothermia
    - Preexisting hypertension
  - Vasoconstriction from exogenous catecholamines
  - Aortic stenosis
  - Idiopathic hypertrophic subaortic stenosis
- Myocardial depression
  - Uncorrected mechanical lesions
    - Incomplete coronary revascularization
    - Valvular stenosis or insufficiency
    - Mechanical valve malfunction
  - Functional depression (lasts □24 h)
  - Coronary spasm
  - Inadequate myocardial protection intraoperatively
    - Myocardial edema
    - Myocardial ischemia
    - Myocardial necrosis-infarct
- Metabolic derangement
  - Hypocalcemia
  - Hypomagnesemia
  - Hypoxia
  - Acidosis
- Arrhythmias
- Conduction defects
- Tamponade
- Pharmacologic depression
  - Anesthetic agents
  - Quinidine
  - Procainamide
  - Lidocaine
  - Beta-blockers
  - Calcium channel blockers

Treatment of Low Cardiac Output

Low CO in the postoperative period is associated with a higher incidence of respiratory, renal, hepatic, and neurologic failure. Treatment of low CO first requires an analysis of possible causes (Table 148.1). Operative complications, such as coronary graft closure, inadequate revascularization, poor myocardial protection, valve malfunction, or paravalvular leak, can cause pump dysfunction. Graft closure or acute coronary occlusion can have immediate hemodynamic effects (a fall in CO and a rise in left-sided filling pressures). Early graft failures are usually due to technical factors, but perioperative myocardial infarction due to coronary spasm can also occur in operated or in nonoperated vessels [20]. When the diagnosis of spasm is entertained and ST-segment changes as well as wall motion abnormalities occur, aggressive management with nitroglycerin and diltiazem should be instituted [21]. If these drugs are unsuccessful in reversing the hemodynamic deterioration, cardiac catheterization or reexploration, or both, inspection of the grafts should be considered [22]. Myocardial depression can be seen in the first 24 hours as a result of the operation. Common causes of perioperative pump dysfunction include arrhythmias, tamponade, hypovolemia, myocardial infarction, systemic acidosis, electrolyte imbalance, and hypoxia.

Early graft patency is an important determinant of postoperative ventricular function and performance on stress tests. On the other hand, the occurrence of perioperative myocardial infarction without hemodynamic compromise has not been shown to be significantly related to graft patency, late survival, or cardiac performance status [23]. The treatment of perioperative infarction consists of therapy to maintain CO, including afterload reduction, especially with nitroglycerin and beta-blockade, if tolerated.

If an obvious cause of low CO is not identified, a systematic approach toward optimizing pump function should be undertaken (Table 148.2). An easy way to organize this approach is by examining preload, afterload, rate, contractility, and rhythm. Because CO is the product of SV and HR (CO = SV ∞ HR), either can be increased.

On arrival to the ICU, many patients exhibit intravascular volume depletion, despite an increase in total body water. The rewarming that is actively done during the early postoperative period causes progressive peripheral vasodilatation and relative

TABLE 148.2

TREATMENT OF LOW CARDIAC OUTPUT

Treat or exclude complications
Valve malfunction (reoperate)
Coronary graft occlusion (reoperate)
Tamponade (reoperate)
Bleeding (reoperate)
Coronary spasm (nifedipine, 10 mg sublingually)
Treat arrhythmias by optimizing heart rate
Increase rate to 90–100 beats/min
Atrial pacing if no heart block
Atrioventricular pacing if heart block
BP (systolic) ≥ 100, or BP (MAP) ≥ 85
Low LAP (< 15 mm Hg)
Give volume (packed cells) if Hct < 25%
Give Ringer's lactate or hetastarch if Hct ≥ 25%
Continue stepwise treatment with volume and dilators until cardiac index adequate (≥ 2.5); do not allow LAP to remain > 15 mm Hg or BP to remain < 100
High LAP (≥ 15 mm Hg): Begin nitroprusside[a] or nitroglycerin, 0.2–0.6 µg/kg/min and increase until desired effect obtained
BP (systolic) < 100 or BP (MAP) < 85
Low LAP (< 15 mm Hg)
Give volume (packed cells) if Hct < 25%
Give Ringer's lactate or hetastarch if Hct ≥ 25%
High LAP (≥ 15 mm Hg): if BP still low
Give epinephrine 2–5 µg/min; increase gradually to 10 µg/min maximum; dobutamine, milrinone
When BP ≥ 100, begin nitroprusside,[a] 0.2–0.6 µg/kg/min; increase until desired effect obtained

[a] See text for alternative drugs.
Note: If BP and cardiac output still low, insert intra-aortic balloon pump.
BP, blood pressure; Hct, hematocrit; LAP, left atrial pressure; MAP, mean arterial pressure.

hypovolemia. The goal MAP is 70 to 80 mm Hg [13]. Normovolemia is essential and can be accomplished with autotransfusion, normal saline, lactated Ringer's solution, albumin (25% solution), or hydroxyethyl starch (hetastarch). In the Saline versus Albumin Fluid Evaluation (SAFE) study involving almost 7,000 patients, albumin had no proven advantage over crystalloids in critically ill patients, although a larger volume of crystalloid is necessary compared to colloid [24]. Hetastarch can provide volume expansion for more than 24 hours. At doses more than 20 mL per kg, it can cause a decrease of factor VIII levels and platelets. Urticarial and anaphylactoid reactions as well as pancreatitis can occur with the use of this product [25].

In addition to ensuring adequate volume resuscitation, clinician should optimize cardiac rate and rhythm. Ventricular filling occurs during diastole and is augmented by a properly timed atrial contraction. If the heart rate is excessive to the extent that there is inadequate time for ventricular filling, cardiac output will be affected. This is particularly true of the hypertrophied or pressure overloaded ventricle and a heart rate of 90 to 100 beats per minute is optimal [13]. After cardiac surgery, atrial fibrillation, sinus bradycardia, and varying degrees of heart blockage can occur. These arrhythmias are usually transient and may be related to perioperative beta-blockade, hyperkalemic damage during the administration of cardioplegia, or unprotected ischemia of the conduction system [26]. Permanent injury to the conduction system is usually the result of surgically induced trauma.

Temporary atrial and ventricular wires are placed at the time of surgery and can be used to maintain CO. Simple atrial pacing (at a rate of 80 to 100 beats per minute) for the treatment of sinus bradycardia may effectively augment CO. Atrial pacing can aggravate a first-degree heart blockage and introduce an atrioventricular dyssynchrony. In this situation, atrioventricular sequential pacing should be attempted. The optimal atrioventricular interval is usually in the range of 100 to 175 milliseconds, depending on the HR. The advantage of atrial pacing over atrioventricular sequential pacing is the maintenance of the normal anatomic pattern of ventricular activation. Loss of the normal sequence of activation depresses ventricular function by approximately 10% to 15%.

Although a low MAP is most common, occasionally one must lower excessive afterload to improve cardiac output. Decreasing systemic vascular resistance (SVR) decreases the heart's oxygen demand. In patients with relatively normal LV function, nitroprusside reliably decreases SVR and increases CO, whereas nitroglycerin may lower CO, perhaps as a result of too great a decrease in cardiac preload (left atrial pressure).

The PV relationship of the left ventricle can be used to predict improvements in stroke volume secondary to reductions in afterload. The therapeutic results depend on the inotropic state of the ventricle. Ventricles with the poorest contractility benefit the most from afterload reduction. If the ventricle is operating on an end-systolic PV relationship with a shallow slope (depressed contractility), reducing afterload (and end-systolic pressure) results in a relatively large increase in SV (Fig. 148.3).

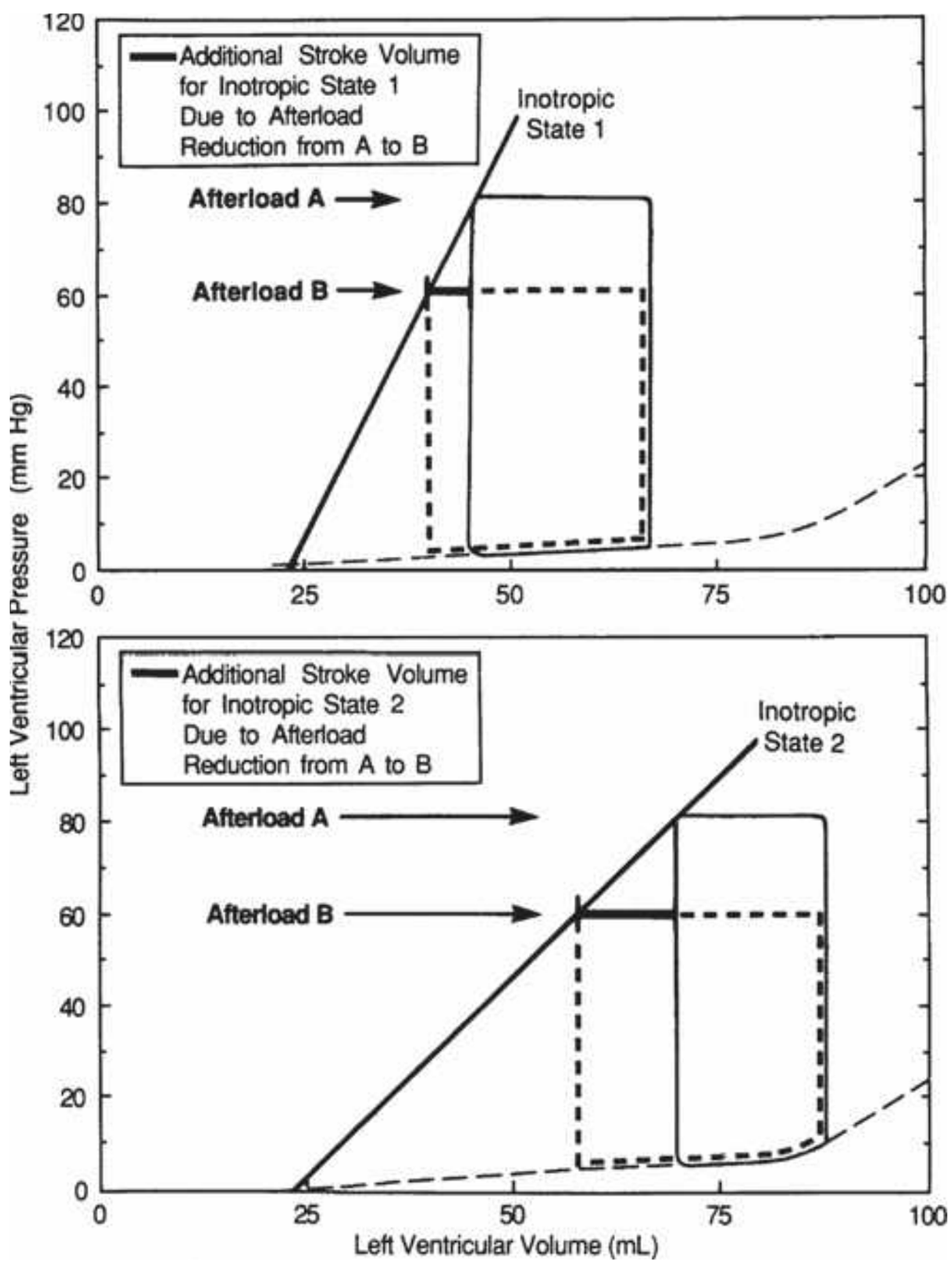

FIGURE 148.3. The improvement in stroke-volume that can be achieved with a reduction in afterload (and consequently, a reduction in end-systolic pressure) depends on the inotropic state of the myocardium. There is more to be gained by afterload reduction in a ventricle with depressed inotropic state (a smaller slope of the end-systolic pressure-volume relationship).

TABLE 148.3

VASODILATORS USED IN POSTOPERATIVE CARDIAC SURGERY PATIENTS

Drug	Dosage range[a]	Activity						
		Arterial	Venous	Onset	Duration	Mechanism	Comments	Toxicity
Nitroprusside (Nipride)	0.2–5.0 µg/kg/min	+3	+2	Immediate	Immediate	Direct vasodilator	May increase myocardial ischemia	Cyanide and thiocyanate
Nitroglycerin	0.3–5.0 µg/kg/min	+1	+4	Immediate	30 min	Direct vasodilator	Improves myocardial ischemia	—
Clevidipine	2–6 mg/h	+3	−	Immediate	Immediate	Direct vasodilator	Low incidence of side effects in comparison to other vasodilators	
Hydralazine	5–10 mg IV	+4	0	15–30 min	2–6 h	Direct vasodilator	Reflex increases cardiac output and heart rate; may cause angina in ischemic heart	None short term
Enalaprilat	10–20 mg IM 0.625–1.25 mg IV	+4	0	20–80 min 15 min	4–6 h	Angiotensin-converting enzyme inhibition	Use cautiously with renal impairment	May cause hyperkalemia; rare angioedema

[a]Initiate treatment at low end of dosage range.

Afterload reduction is also beneficial when residual mitral regurgitation and aortic insufficiency are present.

The postoperative patient with a low CO and an adequate blood pressure may benefit from afterload reduction using incremental doses of nitroprusside. Cardiac index and SV rise as filling pressures and blood pressure fall. Nitroprusside must be used with caution because of its potential for causing cyanide or thiocyanate poisoning, or both. Nitroprusside infusions generally should not exceed 8 µg per kg per minute (Table 148.3). In the presence of ischemia or an acute myocardial infarction, nitroglycerin increases regional myocardial flow and decreases ischemic ST segments toward normal, whereas nitroprusside may have an opposite and deleterious effect [27,28]. Improvement in cardiac function with inotropic agents is generally at the expense of increased myocardial oxygen demand. Inotropic agents, therefore, should be used only when manipulation of HR, rhythm, preload, and afterload are ineffective. When LV depression and low output persist, inotropic therapy must be used. A number of drugs and drug regimens can be used, including dopamine, dobutamine, epinephrine, norepinephrine, and amrinone or milrinone (Table 148.4).

Dopamine usually causes a small increase in HR, although in some patients severe tachycardia can be seen. Dopamine increases cardiac index by stimulating β-adrenergic receptors. At doses less than 3 µg per kg per minute, dopamine causes renal, splanchnic, coronary, and cerebral arterial vasodilatation by the activation of dopaminergic receptors. When dopamine is infused at a rate below 7.5 µg per kg per minute, it causes little change in SVR; above this rate, systemic vasoconstriction, due to stimulation of α-adrenergic receptors, increases. The usual dose range for dopamine is 1 to 20 µg per kg per minute.

Dobutamine is a synthetic catecholamine with minimal α-adrenergic activity but pronounced β_1- and β_2-adrenergic activity. It increases CO by increasing ventricular contractility and rate as well as causing peripheral vascular dilatation. For patients with a low CO and marked peripheral vasoconstriction, dobutamine is preferable to dopamine when the latter is used alone. Nevertheless, because dobutamine is a vasodilator, use of this drug in the presence of hypotension may lead to further hypotension. The usual doses for dobutamine are 5 to 20 µg per kg per minute.

Epinephrine is an α-, β_1-, and β_2-receptor agonist. It increases myocardial contractility and rate. It also increases ventricular irritability. Peripherally, its β-mediated effects (vasodilation) predominate at low doses, whereas α-mediated effects (vasoconstriction) predominate at high doses. The usual epinephrine dose is 1 to 10 µg per minute (0.015 to 0.15 µg per kg per minute).

Norepinephrine has α- and β-adrenergic activity. It increases systemic and pulmonary blood pressure myocardial contractility and CO. Internal mammary grafts remain innervated and are responsive to vasoactive drugs; saphenous vein grafts are not. Norepinephrine has been shown to decrease flow in internal mammary grafts less than phenylephrine in the early postoperative period [29]. The usual dosage is 4 to 10 µg per minute (0.06 to 0.150 µg per kg per minute).

Milrinone is an "inodilator," producing a positive inotropic independent of adrenergic stimulation and causing a reduction in systemic and pulmonary vascular resistance. Milrinone is a phosphodiesterase inhibitor that increases intracellular concentrations of cyclic adenosine monophosphate. Milrinone is a bipyridine derivative that is 20 times more potent than amrinone [30,31]. They are usually used as a second-line medication when a low CO persists despite catecholamines. Concomitant use of catecholamines usually offsets any associated vasodilation. The usual dosage of milrinone is a loading dose of 50 µg per kg over 10 minutes, followed by an infusion of 0.375 to 0.75 µg per kg per minute. Administration of milrinone over a period of 10 minutes prevents the vasodilation that is observed with rapid loading [32–34].

Arginine vasopressin may be helpful if hypotension persists despite adequate cardiac output, despite use of vasoactive

TABLE 148.4

INOTROPIC AGENTS USED IN POSTOPERATIVE CARDIAC SURGERY PATIENTS

Drug	Dose range	Activity					
		Alpha	Beta	Onset	Offset (min)	Heart rate[a]	Comments
Dopamine	1–3 µg/kg/min	Plus renal and mesenteric vasodilatation, dopaminergic	Same as alpha	Immediate	Few	Increase of 20%–30% non-dose related (rate: idiopathic increase to 50%–70%)	Minimal PVR at dose < 10 µg/kg/min; renal blood flow at low dose[b]
	1–10 µg/kg/min	+2	+2				
	> 10 µg/kg/min		+2				
Dobutamine	1–10 µg/kg/min	0	+4	Immediate	2–3	25%–30%	Very similar to isoproterenol; tachyphylaxis[b]
Epinephrine	1–2 µg/min	0	+2	Immediate	2–3	+1	Predominant effect varies with dose, marked vasoconstriction at high doses
	2–10 µg/min	+2	+2				
	> 10 µg/min	+2	0				
Norepinephrine	2–16 µg/min	+4	+2	Immediate	2–3	0	Pronounced vasoconstriction increases myocardial work; valuable in vasodilated patient or in use with vasodilator; may reduce renal perfusion, especially at higher doses[b]
Amrinone	10–30 µg/kg/min[c]			2–10 min	60–90	0	Increases output and decreases SVR; no tachyphylaxis; may cause thrombocytopenia
Milrinone	0.375–0.75 µg/kg/min[d]			5 min	2–4 h	+10%	Increases output; decreases SVR, PVR; may increase ventricular ectopic activity
Calcium chloride ($CaCl_2$)	100–200 mg	Restores ionized Ca^{2+} and acts synergistically with inotropic catecholamines	Same as alpha	Immediate	15	0	
Vasopressin	0.1–0.4 U/min			Immediate	Few	0	Works by V1 and V2 receptors to offset vasoplegia

[a]Depends on balance of direct cardiac effect versus reflex effects.
[b]May all decrease endocardial ratio (diastolic pressure time index/systolic pressure time index).
[c]Initiate amrinone with 0.75-mg/kg bolus over 5 min; repeat up to 2 times if necessary. Next, titrate infusion to increase cardiac index 25% to 40%.
[d]Initiate with 50-µg/kg bolus over 5 min.
PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

substances like epinephrine; "vasoplegia" or autonomic failure may be present. Vasopressin levels are low in normotensive patients after cardiac surgery and disproportionately low in patients with "vasodilatory shock." Acting on vascular V1 and renal V2 receptors, in doses ranging from 0.1 to 0.4 U per min, vasopressin can be effective in improving vascular tone. Care in its use must be taken in patients with marginal cardiac output as vasopressin may further compromise splanchnic blood flow [13].

Myocardial depression can occur as a result of excess citrate administration, as seen during massive blood transfusions. Administration of calcium chloride (100 to 200 mg IV) can augment contractility.

Occasionally, CO remains inadequate even after preload, afterload, and contractility are optimized. Additional energy can be added to the system by mechanical support. The most common method to achieve this is by the insertion of an intra-aortic balloon pump (IABP), through a femoral artery. By raising

aortic diastolic pressure, the IABP increases diastolic pressure time index (DPTI). Because the IABP decreases afterload, it allows better ventricular emptying, which decreases LV diastolic pressure, thus further increasing DPTI. Coronary blood flow and CO increase. Proper balloon pump function requires synchronization with the cardiac cycle using the electrocardiogram or intra-arterial pressure tracing. The IABP is inflated with helium (40 mL) at the onset of diastole and deflated at the onset of systole. Weaning is usually accomplished by gradually reducing the proportion of augmented beats from 1:1 to 1:3 or by reducing balloon volume.

The insertion of the IABP is done preoperatively typically for unstable angina, LV failure, or cardiogenic shock. The balloon is inserted intraoperative mainly because of an inability to wean from bypass. The IABP has a high complication rate; these complications include aortic dissection, arterial perforation, femoral artery occlusion or thrombosis with leg ischemia, arterial emboli, and wound infection [35]. Although extremely rare, spinal cord ischemia resulting in paraplegia has been reported [36]. Blood seen in the lumen of the IABP signals rupture of the balloon and requires immediate removal.

Rarely, patients require even more mechanical assistance than can be provided with the IABP. In these cases, an option is the use of an LV-assist device [37,38]. This device pumps blood around the injured left ventricle, something that the IABP cannot do.

Hypotension

Causes of hypotension (MAP less than 70) include those for low CO (see Table 148.1). Therapeutic interventions for hypotension must prevent a catastrophic outcome. Untreated hypotension results in coronary hypoperfusion, arrhythmias, ventricular dysfunction, and death. Other possible causes of decreased afterload include pharmacologic vasodilatation or sepsis. Immediate treatment consists of norepinephrine (approximately 4 to 10 µg per minute) and volume repletion.

Evaluation of hypotension should include measurements of cardiac index, HR, and right and left atrial filling pressures. Hypovolemia presents with low filling pressures and low CO. LV depression presents with high left atrial and, sometimes, right atrial pressures and a very low CO. Bradycardia, especially in the presence of a poorly compliant postoperative ventricle, causes hypotension because the ventricle is unable to compensate by augmenting SV. Treatment of hypotension begins with optimization of rate (Table 148.5). If the rate is too slow, atrial (or, in the presence of complete heart block, atrioventricular) pacing should be used to bring the rate up to 90 to 100, depending on the response. Arrhythmias should be treated promptly (see "Arrhythmias" section of this chapter and Chapters 41–43). Intravascular volume should be optimized. Ventricular filling pressures in the early postoperative patient routinely need to be higher than normal to maximize SV, because the ventricle is stiff and dysfunctional after cardiopulmonary bypass.

TABLE 148.5

MANAGEMENT OF BRADYCARDIA

Diagnosis	Treatment
Sinus or nodal	Atrial pacing at 80–100 beats/min
AV block	AV sequential pacing at 80–100 beats/min (? digoxin toxic)
Atrial fibrillation	Ventricular pacing

AV, atrioventricular.

Echocardiography provides for a real time measure of the filling status of the ventricles. It avoids the pitfalls of a Swan as it can measure volume and does not use pressures as a surrogate for volume. Also right and left sided outputs can be calculated. It provides for a very reliable and quick way to evaluate and treat hypotension.

Tamponade

Cardiac tamponade results from the accumulation of fluid or clotted blood within the mediastinum, creating a restriction for diastolic filling of both ventricles. The findings associated with tamponade in the immediate postoperative period include: (a) elevation and equalization of the central venous pressure, pulmonary diastolic pressure, left atrial pressure (pulmonary artery capillary wedge pressure), and right ventricular diastolic pressure (central venous pressure); (b) low urine output; (c) excessive chest tube drainage; (d) mediastinal widening on chest radiograph; and (e) low CO and hypotension. Echocardiographic findings of tamponade include RV diastolic collapse, right atrial systolic collapse, IVC plethora, and respirophasic changes in transmitral filling.

The treatment for cardiac tamponade is early reoperation. The patient may temporarily respond to some simple supportive measures such as reducing airway pressure, infusing intravascular volume expanders, and providing inotropic support. Myocardial dysfunction and myocardial edema reduce the amount of space occupied by fluid and clot required to cause tamponade physiology [39].

Although cardiac tamponade usually presents within the first 24 hours postoperatively, it can present as a subacute syndrome as late as several weeks following surgery. The symptoms are often nonspecific and can include malaise, low-grade fever, diaphoresis, dyspnea, chest pain, and anorexia. Transesophageal or transthoracic echocardiography may demonstrate retained clot and blood or wall abnormalities characteristic of tamponade (diastolic collapse of the right atrium and right ventricle). On occasion, right-sided heart catheterization may be necessary to establish the diagnosis (equalization and elevation of filling pressures).

Hypertension

Postoperative hypertension frequently occurs after coronary artery bypass grafting in patients with good LV function, or after corrective surgery for aortic stenosis or idiopathic hypertrophic subaortic stenosis. Postoperative hypertension is a common problem in patients with a history of hypertension. Other causes of hypertension may also involve hypoxemia, hypercarbia, shivering, or anxiety. Hypertension is deleterious because it increases myocardial work and it increases wall tension that may result in rupture of aortic suture lines. The treatment of choice for systolic blood pressures higher than 150 mm Hg is nitroprusside. Beta-blockers can be added for additional blood pressure reduction.

In some patients with a hyperdynamic left ventricle (normal SV and increased peripheral resistance), sodium nitroprusside treatment may be ineffective. In this group, nitroprusside reduces peripheral vascular resistance, which causes reflex sympathetic stimulation. This unmasks the underlying hyperdynamic heart, and SV, pulse pressure, and HR increase [40,41].

Beta-blockers are also effective in controlling hypertension in the cardiac surgical patient; esmolol can be given as a 500 µg per kg loading dose and an infusion of 50 to 300 µg per kg per minute [41]. Enalaprilat, 0.625 to 1.25 mg IV, can also be effective. Diuretics are valuable for managing patients with difficult-to-control hypertension. If the hypertension existed

preoperatively, long-term antihypertensive agents should be restarted.

Arrhythmias

Arrhythmias primarily affect CO and blood pressure. At Beth Israel Deaconess Medical Center in Boston, most cardiac surgical patients undergo placement of temporary epicardial pacing wires—two ventricular and two atrial electrodes. The wires are used diagnostically or therapeutically in approximately 80% of patients.

Atrial wires facilitate the diagnosis or conversion of supraventricular tachycardia, especially atrial flutter. By pacing at a rate faster than the intrinsic atrial rate, the atrium becomes entrained. The critical entrainment rate is evidenced by lead II P waves changing from negative to positive. When the critical entrainment rate has been reached for the critical duration (usually 10 to 20 seconds), the atrial pacer may be slowed and then stopped; the atrial rhythm follows the slowing and then converts to sinus rhythm mechanism. The atrial electrical activity can be recorded on a unipolar precordial (V) lead while standard limb leads are in place; the atrial wires can be attached to the right and left arm leads (with standard leg leads in place) and the electrical signals recorded on a bipolar lead (I) or unipolar leads (II or III). Homogeneous atrial flutter with an atrial rate of 240 to 340 breaks more easily than a more rapid atrial flutter [37,38].

The primary use of the pacing wires postoperatively is to increase a slow HR (see Table 148.5). For sinus bradycardia, atrial pacing should be used. For a junctional slow rhythm, atrial pacing should be tried, but if any atrioventricular block exists, sequential atrial and ventricular pacing are necessary. For complete heart block, sequential atrial and ventricular pacing should be used. Postoperatively, CO is higher with atrial than with ventricular pacing. In patients with LV hypertrophy, the difference may be as great as 40% [42], because these patients have a greater need for atrial systole to fill the poorly compliant, hypertrophied ventricle.

TREATMENT OF SPECIFIC ARRHYTHMIAS

Ventricular arrhythmias can be caused by myocardial ischemia, hypokalemia, hypomagnesemia, hypoxia, acidosis, sympathetic stimulation, or irritation related to malpositioned intracardiac catheters. Initial treatment should be directed at eliminating any of the triggering factors. Atrial pacing at a more rapid rate may exceed the rate of firing of an ectopic ventricular focus and then suppress its emergence. In the early postoperative period, ventricular ectopy often occurs when the serum potassium concentration is in the low normal range. Keeping the potassium concentration between 4.5 and 5.0 mEq per L and the magnesium more than 2 mEq per L tends to suppress ectopic beats [43,44]. It is not necessary to treat isolated premature ventricular contractions (PVCs) because they are most likely benign. However, if PVCs are more than six per minute, multifocal, or present in salvos of three or more consecutive beats, treatment is then necessary. The easiest therapy for PVCs is atrial pacing at a rate faster than the patient's baseline. Amiodarone bolus IV, followed by an IV infusion usually suppresses them. Among the risks of treatment are the proarrhythmic effects of most available agents [45].

Ventricular tachycardia (VT) can occur at a relatively slow rate and depress blood pressure minimally, or it can occur at a rapid rate, leading to severe LV depression. In either case, VT can degenerate into ventricular fibrillation. When VT markedly depresses blood pressure, direct current cardioversion should be performed immediately. Cardioversion should be performed using a synchronized (with the QRS) mode with 200 J, escalating if necessary to 400 J. In hemodynamically stable patients, lidocaine or amiodarone sometimes terminates VT and obviates the need for cardioversion (see Chapter 6).

TABLE 148.6

MANAGEMENT OF VENTRICULAR ARRHYTHMIAS

Diagnosis	Treatment
Premature ventricular contractions	Atrial pacing to suppress automatic focus; Amiodarone bolus, plus drip; keep K^+ 4.5–5.0; eliminate acidosis; $Mg^{2+} > 2$
Ventricular tachycardia	If BP adequate: Amiodarone bolus plus lidocaine drip; keep K^+ 4.5–5.0; eliminate acidosis ischemia; if tachycardia persists, electrical cardioversion $Mg^{2+} > 2$ If BP low: immediate electrical cardioversion, followed by lidocaine; maintain K^+ 4.5–5.0; amiodarone, 150 mg IV over 10 min
Ventricular fibrillation	Immediate defibrillation

BP, blood pressure.

Ventricular fibrillation is fatal if not treated immediately. This arrhythmia mandates immediate electrical defibrillation (asynchronous mode) using the same energy levels mentioned above (see Chapter 6). An overall approach to ventricular arrhythmias in the postoperative cardiac surgery patient is found in Table 148.6. Amiodarone by IV administration may be useful in the treatment and prophylaxis of ventricular fibrillation or tachycardia.

Supraventricular tachycardias occur commonly during the first few postoperative days. They develop in 11% to 40% of patients after coronary bypass grafting and more than 50% of patients after valvular surgery [46]. Premature atrial contractions may progress to either atrial flutter or atrial fibrillation. These arrhythmias occur in 25% to 33% of postoperative cardiac surgical patients and may be due to unprotected atrial ischemia, atrial stretch, administration of hyperkalemic cardioplegic solutions, or pericarditis secondary to surgery [47]. Prophylactic treatment of all post–heart surgery patients with beta-blockers reduces the incidence of atrial fibrillation [48–50]. Patients who were taking beta-blocking agents preoperatively benefit more from beta-blocker prophylaxis than do those who were not taking beta-blockers before operation. Most recently, the Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR) data demonstrated that oral amiodarone prophylaxis of atrial tachyarrhythmias after cardiac surgery is effective [51].

Atrial fibrillation is the most common arrhythmia affecting patients in the postoperative period and is more common in the elderly and those undergoing valvular surgery. Other supraventricular tachycardias can also affect the patient during the first 24 to 36 hours after surgery. When junctional tachycardia occurs, the rapid rate causes inadequate ventricular diastolic filling. In addition, the lack of a normal atrioventricular delay causes mitral and tricuspid regurgitation, because the ventricles contract before the mitral and tricuspid valves have closed. For atrial fibrillation, the class I recommendation of the American College of Cardiology practice guidelines is to administer AV

nodal blocking agents [52], such as diltiazem or a beta-blocker. Use of beta-blockers must be done with care particularly in the immediate postoperative period when myocardial function is still compromised. Despite the current recommendation, the mainstay of treatment is conversion to and maintenance of sinus rhythm with amiodarone (150 mg IV over 10 minutes followed by an infusion of 1 mg per minute for 6 hours and then 0.5 mg per minute for 6 hours) (13 IV ibutilide, a class III potassium channel blocker, can also acutely convert atrial fibrillation or flutter after cardiac surgery) [49].

Atrial flutter often can be treated effectively with atrial overdrive pacing, using the atrial epicardial electrodes (usually at rates of 350 to 400 beats per minute). Atrial fibrillation ordinarily cannot be treated using overdrive pacing. Indeed, atrial fibrillation can be induced when these techniques fail to convert atrial flutter to sinus rhythm. The ventricular response to atrial fibrillation, however, is sometimes slower and better tolerated than that of the ventricular response to atrial flutter. Pharmacologic therapy for atrial flutter has two goals: (a) blockade of the atrioventricular node to decrease ventricular response and (b) conversion to sinus rhythm. IV diltiazem (10 to 20 mg, followed by 5 to 15 mg per hour) or esmolol (500 µg per kg loading dose and an infusion of 50 to 300 µg per kg per minute) slows the rate by increasing the degree of atrioventricular block. Esmolol may be more effective in restoring sinus rhythm [53]. Beta-blockers and calcium channel blockers should not be used concomitantly. Procainamide (see Chapter 42) may convert the rhythm to sinus mechanism. If pharmacologic therapy fails to convert atrial flutter, electrical cardioversion can be used [54]. An overall approach to supraventricular and ventricular arrhythmias as well as common drug therapy for rate control in the postoperative cardiac surgery patient is found in Table 148.7.

Respiratory System

Respiratory dysfunction can complicate the postoperative course in approximately 8% of cardiac patients. Cardiac surgery reduces functional residual capacity, causes atelectasis [55], increases shunting, and decreases arterial oxygenation. The alveolar–arterial oxygen tension gradient typically widens on the day of and the day after surgery, but then the gradient usually narrows. A positive end-expiratory pressure (PEEP) of 5 cm H_2O helps to restore functional residual capacity toward normal [56].

Most cardiac surgical patients arrive in the cardiac surgical ICU requiring mechanical ventilation (see Chapter 58). The initial ventilator settings are typically as follows: rate, 8 to 10 breaths per minute; fractional inspired oxygen (FIO_2) concentration, 1.0; tidal volume, 6 ml per kg predicted body weight. Lung protective ventilation is recommended in patients with established acute lung injury [57]. After the first set of arterial blood gas measurements returns, the FIO_2 is decreased to maintain the oxygen pressure at 80 to 100 mm Hg; minute volume is regulated to keep carbon dioxide pressure at approximately 40 mm Hg. Oxygen consumption and carbon dioxide increase as the patient warms. PEEP is added as needed to keep FIO_2 below 0.5. High levels of PEEP may be necessary when there is a large intrapulmonary shunt.

Patients should be extubated in the first 6 hours post routine cardiac surgery, unless specific hemodynamic concerns apply. Sato and colleagues have demonstrated extubation within is feasible (9.5%) with low complications in on pump CABG'S. Extubation within the first few hours postoperatively can be done in most patients with good LV function without significant valvular disease and uneventful weaning from cardiopulmonary bypass. If hemodynamic instability is present, controlled ventilation allows better control of arterial pH and carbon dioxide pressure as well as more vigorous fluid administration without as much worry about adverse pulmonary effects. In the presence of excessive mediastinal bleeding, continued mechanical ventilation permits a smoother return to the operating room if re-exploration is necessary (see the section Bleeding).

A complete discussion of management of mechanical ventilation (e.g., initiation and discontinuation) can be found in Chapters 58, 59, and 60. Contraindications to weaning from mechanical ventilation include unstable hemodynamics, excessive bleeding, severe acid–base abnormalities, unstable arrhythmias, and patients who are still warming. In patients who are doing well from cardiac and respiratory standpoints, the presence of an IABP is not a contraindication to weaning and extubation.

Some patients arriving in the cardiac surgical ICU may have undergone minimally invasive procedures such as single-vessel bypass grafting through a small anterior thoracotomy [59]. These patients typically have been extubated in the operating room. They may have more pain than patients who have undergone a standard median sternotomy and have a need for careful balance of pain relief against respiratory depression. They may also have areas of myocardium that have not been revascularized.

Rarely, the postoperative course is complicated by fulminant, noncardiogenic pulmonary edema. Left atrial pressures are low, and the protein content of the edema fluid is high—70% to 96% that of plasma [60]. Some patients may present with "postpump syndrome." In its most severe form, these individuals have a coagulopathy, pulmonary dysfunction with hypoxia, renal and cerebral insufficiency, and a diffuse inflammatory response that is characterized by increased capillary permeability and leakage of fluid into the interstitial space with diffuse edema, fever, and leukocytosis. The cause of these derangements may be activation of complement (C3 and C5) during cardiopulmonary bypass [61,62]. Various drugs have been implicated, including protamine and plasma protein fractions [62].

The phrenic nerve may be injured at the time of surgery by surgical manipulation and by cooling [63]. In a patient with good pulmonary function preoperatively, the postoperative course is not affected. However, in the patient with marginal

TABLE 148.7

MANAGEMENT OF SUPRAVENTRICULAR ARRHYTHMIAS

Diagnosis	Treatment
Premature atrial contractions	Atrial pacing at faster rate
Atrial flutter	If markedly BP or ischemia: DC cardioversion, followed by Amiodarone If BP adequate and no ischemia: Amiodarone overdrive pacing; if heart rate > 120 beats/min; diltiazem or esmolol to slow
Atrial fibrillation	If markedly ↓ BP or ischemia: DC cardioversion, followed by Amiodarone If BP adequate and no ischemia Amiodarone; if heart rate > 120 beats/min, diltiazem or esmolol

↓, low; BP, blood pressure; DC, direct current.

reserves, prolonged ventilatory support may be necessary. Poor diaphragmatic function must be suspected if there is paradoxic breathing when weaning, elevated diaphragm on chest radiograph, or decreased vital capacity. The diagnosis can usually be made with fluoroscopy.

Renal System

Renal function is, in many respects, a reflection of cardiac function. The risk factors commonly seen in acute renal failure include: (a) preoperative renal failure, (b) diabetes mellitus, (c) postoperative hypotension, (d) old age, and (e) prolonged operation. With adequate CO, most post-cardiac surgical patients have a high urine output, usually more than 50 mL per hour.

Many patients exhibit a marked diuresis in the immediate postoperative period with urine outputs of 200 to 500 mL per hour. The cause of this diuresis is multifactorial. Hypothermia diminishes flow to the outer renal cortex, decreases the free water clearance, and increases the filtration fraction [64]. Atrial distention may promote the release of atrial natriuretic factor and inhibit the release of vasopressin. A marked diuresis is generally not seen in those patients who have acute reductions in chronically elevated left atrial pressures [65].

Salt and water, accumulated during the intraoperative and early postoperative periods, are excreted over the first several days postoperatively. In patients who have good LV function, the diuresis usually begins on the second postoperative day.

Renal failure following heart surgery occurs in approximately 7% of post-cardiac patients. It carries a high mortality rate—27% to 47% [66,67]. Factors that increase the risk of perioperative renal failure include exposure to contrast media, perioperative use of aminoglycosides, nonsteroidal anti-inflammatory agents, or angiotensin-converting enzyme inhibitors.

Bleeding

Bleeding is a common problem after cardiac surgery and can be surgical or nonsurgical in nature. Persistent surgical bleeding may require reoperation. Nonsurgical bleeding can be multifactorial. Common causes include residual heparin activity, abnormal clotting factors, uncontrolled fibrinolysis, and thrombocytopenia. A careful history provides the best clue to intrinsic bleeding problems. Patients taking aspirin or antiinflammatory drugs usually have some degree of platelet dysfunction. Screening tests include PT, PTT, platelet count, and bleeding time. Specific abnormalities require further evaluation and correction before elective heart surgery is performed (see Chapters 108 to 109).

Intraoperative factors can predispose to bleeding. Inadequate heparin administration results in excessive consumption of clotting factors. Inadequate neutralization of heparin with protamine leaves residual heparin activity. Improved titration of heparin and protamine can be achieved by assaying heparin activity either indirectly with an activated clotting time or directly with a heparin analyzer [68,72]. Prolonged cardiopulmonary bypass causes platelet dysfunction and depletion and dilution of clotting factors. Disseminated intravascular coagulation occurs rarely, whereas a substantial body of evidence suggests that some primary fibrinolysis occurs routinely during cardiopulmonary bypass (see Chapter 108). We routinely use Tranexamic acid—intraoperatively at our institution.

A standard battery of screening tests enables an assessment of postoperative clotting mechanisms. For abnormal bleeding workup, we routinely obtain a PT, PTT, platelet count, and thrombin time (TT). When the TT is prolonged, a reptilase time distinguishes between excess heparin and fibrinolysis or consumption. A systematic analysis of clotting disorders may be based on the information given in Table 148.8. Platelets may

TABLE 148.8

EXCESSIVE BLEEDING FROM CLOTTING ABNORMALITIES IN THE POSTOPERATIVE CARDIAC SURGERY PATIENT

Cause	Tests							
	PT	PTT	TT	Platelet count	RT	FIB	FSP	Treatment
Heparin excess	N			N	N	N	N	Protamine sulfate titrated with activated clotting time or heparin assay
Excessive primary fibrinolysis		N–Sl		N		N		EACA, 4–8 g IV over 10 min followed by 1 g/h infusion for 5–8 h (until clotting factors N); FFP to regulate clotting factors
Compensated[a]	N							
Uncompensated[a]			N					
Excessive consumption[b]								Treat cause: FFP, cryoprecipitate, platelets
Thrombocytopenia or platelet dysfunction[c]	N	N	N		N	N	N	Platelets
Undefined[d]	Sl		Sl	N	N	N	N	FFP, cryoprecipitate, ? EACA

[a] *Compensated* refers to a minor fibrinolysis under which the body can keep up with the deficiencies; *uncompensated* refers to a rapid process under which the body cannot keep up with the fibrinolysis.
[b] Rare excessive consumption (also known as *disseminated intravascular coagulation*) always has associated secondary fibrinolysis.
[c] Platelets may be reduced in function as well as number.
[d] This group, probably of mixed etiology, occurs frequently.
EACA, epsilon-aminocaproic acid; FFP, fresh-frozen plasma; FIB, fibrinogen; FSP, fibrin-split products; N, normal; PT, prothrombin time; PTT, partial thromboplastin time; RT, reptilase time; Sl, slightly; TT, thrombin time.

be deficient in function as well as in number; cardiopulmonary bypass causes both defects [69].

Treatment is based on the diagnosis, although the diagnosis may not be straightforward because the pathogenesis of abnormal clotting may be mixed. Residual heparin effect is a common problem. Although heparin is fully reversed after the operation, heparin rebound can occur as heparin that was stored in body fat elutes into the blood. Heparin rebound is the most common cause of prolonged PTT and TT [70–72]. A normal reptilase time establishes this diagnosis, and additional protamine treats it.

Excessive primary fibrinolysis and excessive consumption may be indistinguishable by the tests listed, although the latter condition is usually characterized by a lower platelet count. Treatment of disseminated intravascular coagulation should be aimed at its cause. Treatment of primary fibrinolysis consists of repleting clotting factors and infusing an antifibrinolytic agent, epsilon–aminocaproic acid. Cryoprecipitate is the cold insoluble protein fraction of plasma that is rich in factor V, factor VIII, von Willebrand factor, and fibrinogen. It is more concentrated than fresh-frozen plasma, but, because it is a pooled product, it carries a higher risk of transfusion-related infection.

When platelet dysfunction is suspected, either on the basis of preoperative aspirin intake or prolonged cardiopulmonary bypass, platelets should be transfused. Platelet transfusion should be considered in any patient with a platelet count of 100,000 per mm^3 who continues to bleed despite aggressive procoagulant therapy [71,72].

In some centers, PEEP is used to help control bleeding after cardiac surgery. Some studies have shown a marked diminution of bleeding with levels of PEEP from 10 to 20 cm H_2O [73,74]; others have not [75].

The definition of *excessive bleeding* varies with each patient. As a general guideline, however, bleeding is excessive when drainage from chest tubes is more than 400 mL per hour for the first hour, 300 mL per hour for the first 2 hours, 200 mL per hour for the first 3 consecutive hours, or 100 mL per hour over the first 6 hours. A sudden increase in bleeding suggests an arterial source and mandates re-exploration. Bleeding that is sufficient to cause marked hypotension or tamponade also requires re-exploration. Massive bleeding necessitates emergency re-exploration, regardless of any clotting abnormalities [76,77].

When bleeding is so rapid that cardiac arrest is imminent, the patient should *not* be brought back to the operating room to control bleeding. Instead, the sternotomy should be reopened immediately in the ICU and digital pressure must be applied on the obvious site of bleeding. Transfusions are administered to increase blood volume and blood pressure. Then the patient is transferred to the operating room for definitive control of the bleeding [76,77].

The use of autotransfusion has reduced requirements for transfusing homologous blood. Blood for autotransfusion can be collected in a removable chamber that is part of the standard chest drainage system and is reinfused by gravity drainage, much like a homologous transfusion. It has been demonstrated that autotransfused blood is extensively defibrinated [77].

Fever and Antibiotics

Temperature fluctuations are expected after cardiac surgery. Systemic warming before the termination of cardiopulmonary bypass brings the core temperature to 37°C, but cooling subsequently occurs as heat transfers to the cool extremities. Patients routinely have temperatures in the 34°C to 36°C range when they arrive in the ICU. Warming, shivering, and vasodilatation occur during the first several hours. Temperatures in the 38°C to 39°C range should be expected at this time and require no further evaluation. However, fever during subsequent days is abnormal and requires the usual investigation (see Chapter 76).

Prophylactic antibiotics are widely recommended because of the seriousness of infections of the mediastinum, sternum, cardiac suture lines, and prosthetic valves. Although staphylococcal infections are the greatest concern, antibiotics with broad-spectrum coverage are generally used in preference to specific antistaphylococcal antibiotics [78,79]. Antibiotics should be stopped within 2 days; administration for a longer period offers no advantage [80].

One third of all hospital-acquired bacteremias and most candidemias are associated with vascular catheters [80]. Positive cultures are yielded in 1.5% of vascular catheters, and pulmonary artery catheters have the highest rate of colonization (2.1%) [81]. Catheter-related sepsis is most commonly due to coagulase-negative staphylococci and cannot be treated successfully with antibiotics unless the catheter is removed. A 7- to 10-day course of systemic antibiotics is then usually sufficient, although 4 to 6 weeks is necessary for cases of septic venous thrombosis.

Mediastinal infections are seen in approximately 1% of postoperative cardiac surgical patients. Risk factors include long operation, reoperation, low CO, and prolonged mechanical ventilation [82].

Psychological and Neurologic Dysfunction

Severe neurologic dysfunction occurs in 0.5% to 2.0% of coronary artery bypass graft operations. The incidence is higher in open chamber operations (4% to 10%). More commonly, subtle changes occur, such as cognitive dysfunction and ophthalmologic abnormalities. Central and peripheral nervous system dysfunction occur postoperatively. These events may be caused by emboli of air, clot, or other particulate matter [83].

Peripheral neuropathies can occur in the lower extremities and involve the femoral and peroneal nerves. Both neuropathies are preventable. Injuries of the brachial plexus can occur during sternal retraction secondary to compression or penetration of bone fragments [84,85]. Postoperative psychological dysfunction occurs in 40% to 60% of patients. Three types have been described: (a) an organic syndrome, which corresponds to the central metabolic neurologic dysfunction described above, (b) a postcardiotomy delirium, occurring after a lucid interval, and (c) a postcardiotomy depressive syndrome. Multiple risk factors for the latter two syndromes have been identified, including increased use of anticholinergic drugs, elevated preoperative blood urea nitrogen or decreased body weight, decreased body temperature while on cardiopulmonary bypass, and increased magnitude of overall preoperative sickness. Patients undergoing valve operations are affected more commonly than are patients undergoing coronary revascularization. The incidence seems to be higher in the elderly. Postulated pathogenic mechanisms include cerebral microemboli, cerebral red cell sludging, and sensory deprivation [85–88].

Treatment of the depressed patient begins with frequent reassurance and antidepressant therapy. In patients with postcardiotomy delirium, helpful measures include family support, general reassurance, and adequate sleep. Removing the patient from the ICU is desirable. Administration of small doses of IV haloperidol (1 to 2 mg or more) is very helpful in postcardiotomy delirium.

Gastrointestinal Complications

Gastrointestinal complications occur in approximately 1% of patients undergoing cardiac surgery. Patients with low CO and multiple organ failure are more prone to developing gastric and

duodenal bleeding (see Chapters 91, 92). Other gastrointestinal complications include cholecystitis, pancreatitis, intestinal obstruction, or ischemia. These complications can occur anytime from 2 days to 4 weeks after operation. A nasogastric tube is placed in the operating room and used routinely to prevent postoperative gastric distention. In most cases, the tube can be removed on the first postoperative day after endotracheal extubation.

Bowel ischemia and bowel infarction can be caused by embolism or low mesenteric flow. Emboli can originate from the heart, from an atherosclerotic aorta, or from suture lines communicating with the systemic circulation. Atrial fibrillation predisposes to the formation of atrial thrombi and embolization. Low CO, α-adrenergic pressors, and digoxin all increase the risk of low mesenteric flow (see Chapter 151). When bowel ischemia or infarction is suspected, laparotomy should be performed urgently.

To prevent upper gastrointestinal ulceration and bleeding, the gastric pH should be maintained above 4.0. Histamine-2–blockers or proton pump inhibitors and antacids may be required. Sucralfate is an effective prophylactic agent, and because it does not reduce acidity, it may decrease colonization of the upper gastrointestinal tract with Gram-negative organisms [89]. The early institution of enteral feedings may also reduce the incidence of gastrointestinal bleeding and complications. During low CO states, intestinal absorption is not totally suppressed, only delayed [90].

Pancreatitis is a potentially lethal complication of cardiac surgery. Its occurrence is probably related to decreased splanchnic blood flow, and therefore it tends to occur in patients who have associated cardiac complications. In approximately one third of cardiac surgical patients, there is a significant rise in the level of serum amylase (> 300 IU per L) by the second postoperative day [91]. However, clinically overt pancreatitis occurs in only approximately 2% of patients. Nonpancreatic hyperamylasemia is associated with increased mortality. The cause is unknown [92].

Endocrine Complications

Hyperglycemia is the most common endocrine abnormality requiring postoperative management and occurs frequently whether or not there was preexisting diabetes. Van de Berge et al. [93] published data from a mixed medical/surgical patient population of which a majority had undergone cardiac surgery demonstrating a significant reduction in morbidity and mortality for those who had tight glycemic control (at or below 110 mg per dL). However, in a recent study published by the NICE sugar study investigators, it was found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter [94]. During cardiac operations, insulin requirements under hypothermia are low but increase dramatically during rewarming. Insulin requirements usually decrease by the third postoperative day as the stress of surgery diminishes. However, intensive management of diabetes may be necessary when the patient resumes an oral diet. It is not uncommon for non–insulin-dependent diabetics to require insulin at the time of discharge.

Thyroid dysfunction can occur in seriously ill patients who were euthyroid preoperatively. The perioperative determination of thyroid function is difficult because of abnormalities in thyroxine binding and the fact that thyroid-stimulating hormone responds sluggishly to decreased triiodothyronine and thyroxine levels in critically ill patients. Advances in the care of the postoperative cardiac surgery patient, based on randomized controlled trials or meta-analyses of such trials, are summarized in Table 148.9.

TABLE 148.9

SUMMARY OF ADVANCES IN MANAGEMENT OF POSTOPERATIVE CARDIAC PATIENT

- Albumin has no proven advantage over crystalloids for resuscitation in critically ill patients [24].
- Prophylactic use of beta-blockers reduces the incidence of atrial fibrillation [42,49,50].
- The rapid shallow breathing index (RSBI) predicts success in weaning from mechanical ventilation [95].
- Hyperamylasemia occurs in one third of cardiac surgical patients but only 2% develop overt pancreatitis [91].
- Tight glycemic control increases morbidity and mortality [94].
- The routine use of pulmonary artery catheterization does not lead to improved clinical outcomes [5–9].

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CHAPTER 149 ■ NONCARDIAC SURGERY IN THE CARDIAC PATIENT

STEVEN B. EDELSTEIN AND SCOTT W. BYRAM

Much has been written regarding the management of the patient with significant coronary artery disease presenting for noncardiac surgery. As the patient population in the United States continues to age, the issues surrounding risk assessment, perioperative optimization of drug regimens, and evidence-based improvement in overall outcome will persist. This chapter will focus on the issues of risk assessment and the current state of perioperative medical management for the cardiac patient presenting for intermediate- to high-risk surgical procedures.

PATHOPHYSIOLOGY OF PERIOPERATIVE CARDIAC COMPLICATIONS

It is well known that nonfatal perioperative myocardial infarction (MI) is an independent risk factor for subsequent MI and cardiac death within 6 months [1]. It has also been reported that those patients who have cardiac arrest after noncardiac surgery have a significantly elevated hospital mortality rate that has been reported as high as 65% [2].

Much research has been performed to elucidate the etiology of cardiac complications. A recent review of the subject matter by Grayburn and Hillis [3] identified some of the major issues and pathophysiologic changes that surround perioperative cardiac complications. It has become clear that plaque rupture occurs in about half of all perioperative myocardial infarctions [4]. Autopsy series also indicate that acute coronary thrombosis contributes to approximately one third of perioperative ischemic morbidity [5]. In fact, a study that involved patients who underwent coronary angiography prior to vascular surgery revealed that the majority of nonfatal myocardial infarctions occurred in arteries without high-grade stenosis [6].

The remainder of ischemic events appears to be the result of an imbalance between myocardial oxygen supply and consumption in the presence of existing coronary artery disease. It is well known that myocardial supply/demand can be adversely affected by anemia, hypotension leading to tachycardia, hypertension (resulting from postoperative pain or withdrawal of anesthesia), or shifts in intravascular volume. Also, alterations in the inflammatory and coagulation cascades can ultimately play a role in the development of myocardial ischemic events [3,7,8].

Obviously, the causes of perioperative myocardial infarction/ischemia are complex and not clearly elucidated. Devereaux et al. [9] have developed a summary of potential triggers for perioperative elevation in troponin levels, arterial thrombosis, and fatal myocardial infarction. It is also important to note that the majority of perioperative myocardial infarctions occur 1 to 4 days following noncardiac surgery [10] (Fig. 149.1).

DIAGNOSIS OF PERIOPERATIVE MYOCARDIAL INFARCTION IN NONCARDIAC SURGERY

A problem exists when discussing the issues of myocardial infarction and noncardiac surgery. Currently there is no consensus on diagnostic criteria as to what constitutes a perioperative MI in patients undergoing noncardiac surgery. Devereaux et al. [11], to overcome this issue, formulated a proposed diagnostic criterion for perioperative MI. The criteria were adapted from a consensus document of the European Society of Cardiology/American College of Cardiology (ESC/ACC) [12]. These criteria have been summarized in Table 149.1. The criteria rely on biochemical markers such as cardiac troponin, creatine kinase MB (CK-MB), and other objective measures such as

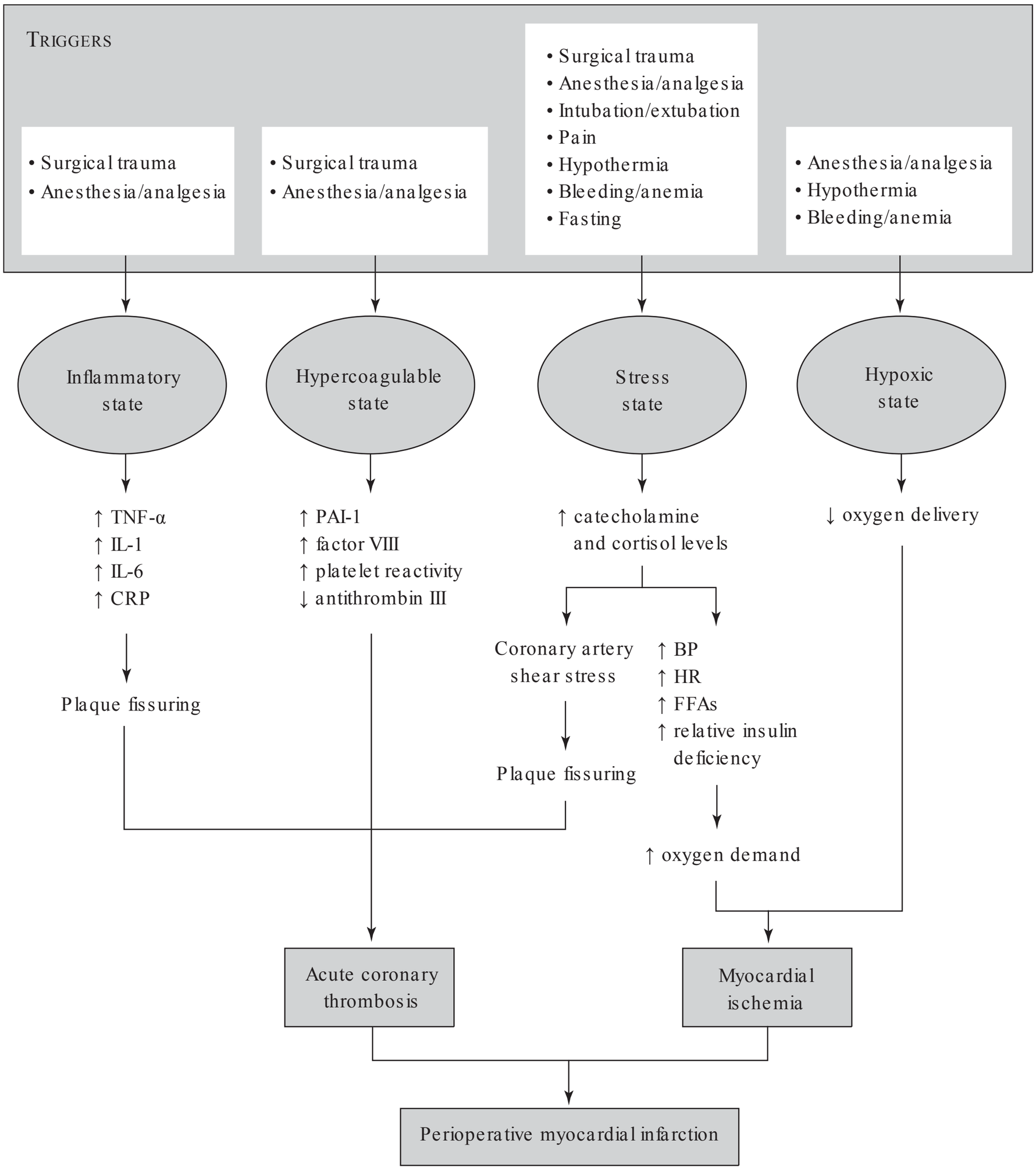

FIGURE 149.1. Potential triggers of states associated with perioperative elevations in troponin levels, arterial thrombosis, and fatal myocardial infarction. BP, blood pressure; CRP, C-reactive protein; FFAs, free fatty acids; HR, heart rate; IL, interleukin; PAI-1, plasminogen activator inhibiter-1; TFN-α, tumor necrosis factor-α. [Reprinted from Devereaux PJ, Goldman L, Cook DJ, et al: Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 173(6):627–634, with permission. © 2000 CMA Media Inc.]

electrocardiogram (ECG) changes and echocardiographic evidence of ischemia.

HISTORY OF RISK ASSESSMENT

For many years, the goal has been to identify a risk assessment tool that would help to identify patients at risk for perioperative cardiac complications. Once identification of this patient subset has been made, interventions could then be performed to reduce the incidence of perioperative myocardial ischemia and infarction [13].

Dripps Index of the American Society of Anesthesiologists

Since the 1960s, the desire to find the optimal tool of risk assessment has been present. The American Society of Anesthesiologists (ASA) developed the Dripps Index as a way not only to identify risk among patient groups, but also to provide a common framework and communication device that could easily be distributed among differing medical specialties [14]. In 1970, Vacanti et al. [15] used the index to predict cardiac death within 48 hours of surgery. Within the five physical status

TABLE 149.1

PROPOSED DIAGNOSTIC CRITERIA FOR PERIOPERATIVE MYOCARDIAL INFARCTION IN PATIENTS UNDERGOING NONCARDIAC SURGERY

The diagnosis of perioperative MI requires any one of the following criterion:

Criterion 1: A typical rise in the troponin level or a typical fall of an elevated troponin level detected at its peak after surgery in a patient without documented alternative explanation for an elevated troponin level (e.g., pulmonary embolism); or a rapid rise and fall of CK-MB only if troponin measurement is unavailable.[a]

This criterion requires that one of the following criteria must also exist:

- Ischemic signs of symptoms (e.g., chest, arm, or jaw discomfort, shortness of breath, pulmonary edema)
- Development of pathological Q waves on ECG
- ECG changes indicative of ischemia
- Coronary artery intervention
- New or presumed new cardiac wall motion abnormality on ECG, or new or presumed new fixed defect on radionuclide imaging

Criterion 2: Pathological findings of an acute or healing MI

Criterion 3: Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

[a]Because CK-MB is both less sensitive and less specific in the perioperative setting compared with other settings and compared with troponin levels, it should be used for diagnostic purposes only when troponin levels are not obtainable.
CK-MB, creatine kinase; MB, isoenzyme; ECG, electrocardiogram; MI, myocardial infarction.
From Devereaux PJ, Goldman L, Yusef S, et al: Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. *CMAJ* 173(7):779–788, with permission. © 2000 CMA Media Inc.

grades identified, perioperative mortality rates range from 0% for ASA status 1 to 9.4% for ASA status 5. However, some of the major drawbacks to the utilization of the ASA score are that it was developed prior to multivariate clinical prediction rules, has limited utility, is very subjective, and is not uniformly reproducible [16].

Goldman Risk Assessment Tool

One of the original cardiac risk assessment tools developed in the 1970s by Goldman was an elaborate attempt to identify those patients at undue risk [17]. Risk assessment was based on several clinical variables. Goldman identified nine independent variables associated with perioperative cardiac events. These are included in Table 149.2, and consist of variables ranging from advanced age to the presence of significant valvular heart disease.

Each variable was assigned specific points and the patients were divided into risk class depending on the number of points generated. The highest classification—class IV (more than 26 points) was associated with a 78% incidence of major cardiac complications in the perioperative period. However, the drawback to use of the tool was the cumbersome nature, making the utilization of the Goldman risk assessment tool somewhat impractical.

TABLE 149.2

GOLDMAN'S NINE INDEPENDENT VARIABLES ASSOCIATED WITH PERIOPERATIVE CARDIAC EVENTS

Age over 70 years
Myocardial infarction in the preceding 6 months
Preoperative third heart sound or jugular venous distention
Significant valvular aortic stenosis
Emergency surgery
Intraperitoneal, intrathoracic, or aortic operation
More than 5 premature ventricular beats per minute documented at any time before operation
Rhythm other than sinus or the presence of atrial premature contractions on preoperative electrocardiogram
One or more markers of poor general medical condition

From Goldman L, Caldera DL, Nussbaum SR, et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 297:845–850, 1977.

Detsky Modification of the Goldman Risk Assessment Tool

In 1986 Detsky attempted to modify the Goldman risk assessment tool by the addition of angina severity and a history of recent pulmonary edema [18]. Broad categories included the variables of coronary artery disease, Canadian Cardiovascular Society Angina Classification, alveolar pulmonary edema, suspected critical aortic stenosis, arrhythmias, poor general medical status, emergency surgery, and age 70 or older. However, just as with Goldman, this risk assessment tool was viewed to be exceedingly cumbersome. It appears that both indices may not have sufficient discriminate power to identify significant coronary artery disease in patients at the lower end of the spectrum of clinical risk [19] and both indices have been refuted or supported by an equal number of studies [20].

Adding to the controversy has been a prospective cohort study that compared the varying risk indices for patients undergoing noncardiac surgery. Gilbert et al. [16] compared 2,035 patients referred for consultation prior to noncardiac surgery and four risk indices: the Dripps Index of the ASA, the original cardiac risk index described by Goldman, the modified Detsky (which had been modified in 1997 by the American College of Physicians by stratifying patients into three risk groups) [21], and the Canadian Cardiovascular Society (CCS) Index for angina level [22]. The most striking finding of the study was that existing cardiac risk prediction methods had a generally poor degree of accuracy.

Eagle Criteria

Eagle et al. [23], while assessing the validity of dipyridamole-thallium stress testing in vascular patients, developed another set of risk criteria for patients undergoing major vascular surgery. The group found five clinical predictors of postoperative cardiac events. These included: presence of Q waves on resting ECG, history of angina, history of ventricular ectopy requiring treatment, diabetes mellitus requiring medical treatment, and age above 70 years. Also on logistic regression, the group noted two independent dipyridamole thallium test predictors of ischemic events that included thallium redistribution and ischemic ECG changes during or after pharmacologic stressing.

Lee Revised Cardiac Risk Index Stratification System

In an attempt to simply the Goldman index, Lee et al. [24] developed the Revised Cardiac Risk Index (RCRI) Stratification System. The RCRI for the first time identified six independent risk predictors associated with cardiac morbidity and noncardiac surgery. These included: high-risk surgery (examples included intraperitoneal, intrathoracic, or suprainguinal vascular reconstruction), a history of ischemic heart disease (excluding previous revascularization), a history of congestive heart failure (CHF), a history of cerebrovascular disease, preoperative treatment with insulin, and a preoperative serum creatinine level more than 2.0 mg per dL (greater than 177 µmol per L).

Cardiac events were determined to be myocardial infarction, cardiac arrest, pulmonary edema, or complete heart block. Four classifications were noted in which risk factors ranged from 0 to 3 or more and correlated to event rate:

- Class I (0 risk factors)—event rate 0.4% (95% confidence interval)
- Class II (1 risk factor)—rate 0.9%
- Class III (2 risk factors)—rate 6.6%
- Class IV (3 or more risk factors)—rate 11.0%

The RCRI has been the most widely accepted risk index, and Romero and de Virgilio [20] have proposed utilizing the RCRI to identify patients who should be treated with strategies to reduce oxygen consumption rather than undergo additional noninvasive testing. They based their recommendations on comments elicited by Bodenheimer [25], who felt that improved outcomes were more likely a result from controlling postoperative myocardial oxygen demand than additional risk stratification.

Miscellaneous Risk Assessment Tools

Other attempts at risk stratification and adjustment are mentioned in the literature. In 2004, Atherly et al. [26] compared the National Surgical Quality Improvement Program (NSQIP), the DxCG, and the Charlson Comorbidity Index. The NSQIP [27] is based on a medical record abstraction of 45 preoperative and 17 intraoperative factors. Factors are multiplied by weights drawn from a model developed using 41,360 patients from the Veteran Affairs Health Care System. Some of the major components of the NSQIP specific to mortality include: ASA class, ventilator dependence, emergency case, age, abnormal albumin, ascites, complexity score, and contaminated wound [28]. In addition to those mentioned earlier, functional status, a history of chronic obstructive pulmonary disease, anemia (hematocrit 38% or less), and elevated white blood cell counts (11,000 or more) are important predictors of morbidity. The ultimate risk score represents the probability of individual patient mortality.

The DxCG uses *International Classification of Disease* (ICD-9) codes, sex, and age to assign a continuous risk score, and the Charlson Comorbidity Index (CCI) was developed to predict empirically the probability of 1-year mortality. The CCI contains 19 categories of comorbidities drawn from the ICD-9 codes. Each of the categories has a weight, which indicates an increase in the risk for 1-year mortality and scores range from 0 to 6.

Atherly et al. [26] found substantial disagreement in the risk assessment calculated by the three methodologies. A weak association was noted between the CCI and DxCG, but neither correlated well with the NSQIP. Overall, the NSQIP was felt to be the best predictor of surgical mortality.

AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION TASK FORCE: PRACTICE GUIDELINES ON PERIOPERATIVE CARDIOVASCULAR EVALUATION FOR NONCARDIAC SURGERY

Practice guidelines serve the purpose of putting forth recommendations based on critically evaluated studies with special emphasis on blinded, randomized, placebo-controlled trial studies. The American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery [29], most recently revised in 2007 (30), begins with the opening statement that the overriding theme of the guidelines was that preoperative intervention was rarely necessary simply to lower the risk of surgery unless such intervention was indicated irrespective of the preoperative context. The desire of the guideline was also to integrate the clinical determinants of risk, the risk of the surgical procedure, and the role of testing into a cohesive format. In addition, the goal of the preoperative consultation was to provide short- and long-term assessment of cardiac risk and avoid unnecessary testing.

Clinical Predictors

One of the major changes in the 2007 revision of the ACC/AHA guidelines is the manner in which risk is assessed. In the 2002 version of the guidelines, risk factors were divided into three groups: major, intermediate, and minor clinical predictors [29]. With the new revision, the minor clinical predictors were removed from the algorithm because, although they may signify risk for coronary disease, they have not been shown to independently increase risk for perioperative cardiac complication [30].

Also changed in 2007, the *major clinical predictors* have been renamed *active cardiac conditions* (Table 149.3). Because of the increasing use of the Revised Cardiac Risk Index created by Lee et al. [24], the committee chose to replace the *intermediate clinical predictors* with five of six risk factors identified by Lee's group. These five risk factors are: history of ischemic heart disease, compensated heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency. The sixth risk factor identified by Lee et al., type of surgery, is addressed elsewhere in the new guidelines.

Functional Capacity

The guidelines also focused significantly on the concept of functional capacity. Functional capacity is best expressed in metabolic equivalent (MET) levels that correlate with specific activities. Basic energy expenditure for activities of daily living (e.g., eating, walking) are around 1 to 4 METs, while strenuous exercise is often more than 10 METs [31]. It has been shown in prior studies that patients unable to obtain a 4-MET demand do poorly in the perioperative period [32] as well as in the long term [33].

Risk of Surgical Procedure

Different surgical procedures are clearly associated with varying amounts of hemodynamic stress. For example, application and release of an aortic cross clamp during abdominal aortic aneurysm repair induces far more physiologic insult than

TABLE 149.3

ACTIVE CARDIAC CONDITIONS FOR WHICH THE PATIENT SHOULD UNDERGO EVALUATION AND TREATMENT BEFORE NONCARDIAC SURGERY (CLASS I, LEVEL OF EVIDENCE: B)

Condition	Examples
Unstable coronary syndromes	Unstable or severe angina[a] (CCS class III or IV[b]) Recent MI[c]
Decompensated HF (NYHA functional class IV; worsening or new-onset HF)	
Significant arrhythmias	High-grade atrioventricular block Mobitz II atrioventricular block Third-degree atrioventricular heart block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR > 100 beats per minute at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia
Severe valvular disease	Severe aortic stenosis (mean pressure gradient > 40 mm Hg, aortic valve area < 1.0 cm^2, or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)

[a]According to Campeau.[9]
[b]May include "stable" angina in patients who are unusually sedentary.
[c]The American College of Cardiology National Database Library defines recent MI as more than 7 days but less than or equal to 1 month (within 30 days).
CCS indicates Canadian Cardiovascular Society; HF, heart failure; HR, heart rate; MI, myocardial infarction; NYHA, New York Heart Association.
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cataract surgery does. Furthermore, recent evidence suggests that major vascular surgery (excluding carotid endarterectomy) may be associated with more than 5% risk for perioperative cardiac death or nonfatal myocardial infarction [30]. With this in mind, the most recent revision of the ACC/AHA guidelines classifies vascular surgery separately as the highest risk group [30] (Table 149.4). Procedures associated with a 1% to 5% cardiac risk, such as orthopedic and intraperitoneal surgeries, are classified as intermediate risk. Most ambulatory surgeries are associated with less than 1% cardiac risk and are classified as low risk.

TABLE 149.4

CARDIAC RISK STRATIFICATION FOR NONCARDIAC SURGERY[a]

Risk stratification	Procedure examples
Vascular (reported cardiac risk often > 5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1%–5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low[b] (reported cardiac risk generally < 1%)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

[a]Combined incidence of cardiac death and nonfatal myocardial infarction.
[b]These procedures do not generally require further preoperative cardiac testing.
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American College of Cardiology/American Heart Association Five Step Algorithm

In the 2007 revision, the authors generated a five-step algorithm for preoperative risk assessment (Fig. 149.2). This was a definite improvement from the somewhat confusing 3-part, 8-step algorithm published in 2002. The simplified recommendations were necessary considering the abysmal (as low as 21%) implementation of the 2002 guidelines [34]. These new guidelines reflect the authors' sentiment in their opening statement that cardiac intervention is not indicated unless it would be performed regardless of a preoperative context. In addition, the algorithm offers recommendations for noninvasive testing and treatment with beta-blockers for selected patients.

Despite these improvements, many authors are still critical of the algorithm. Brett argues that the guidelines are still too ambiguous, referring to the final point of the decision tree: "consider testing if it will change management" [35]. He also makes a point that sometimes noninvasive testing helps patients weigh the risks and benefits of truly elective surgery. In any case, the new algorithm will likely decrease the number of noninvasive test ordered, thus reducing cost and delay in performing elective procedures.

Preoperative Screening ECG

Not long ago it was commonplace to see electrocardiograms in the chart for most surgical patients as part of a preoperative workup. Because these extensive workups were often fruitless, and some testing caused more harm than good, the ASA assembled a task force to develop a practice advisory for

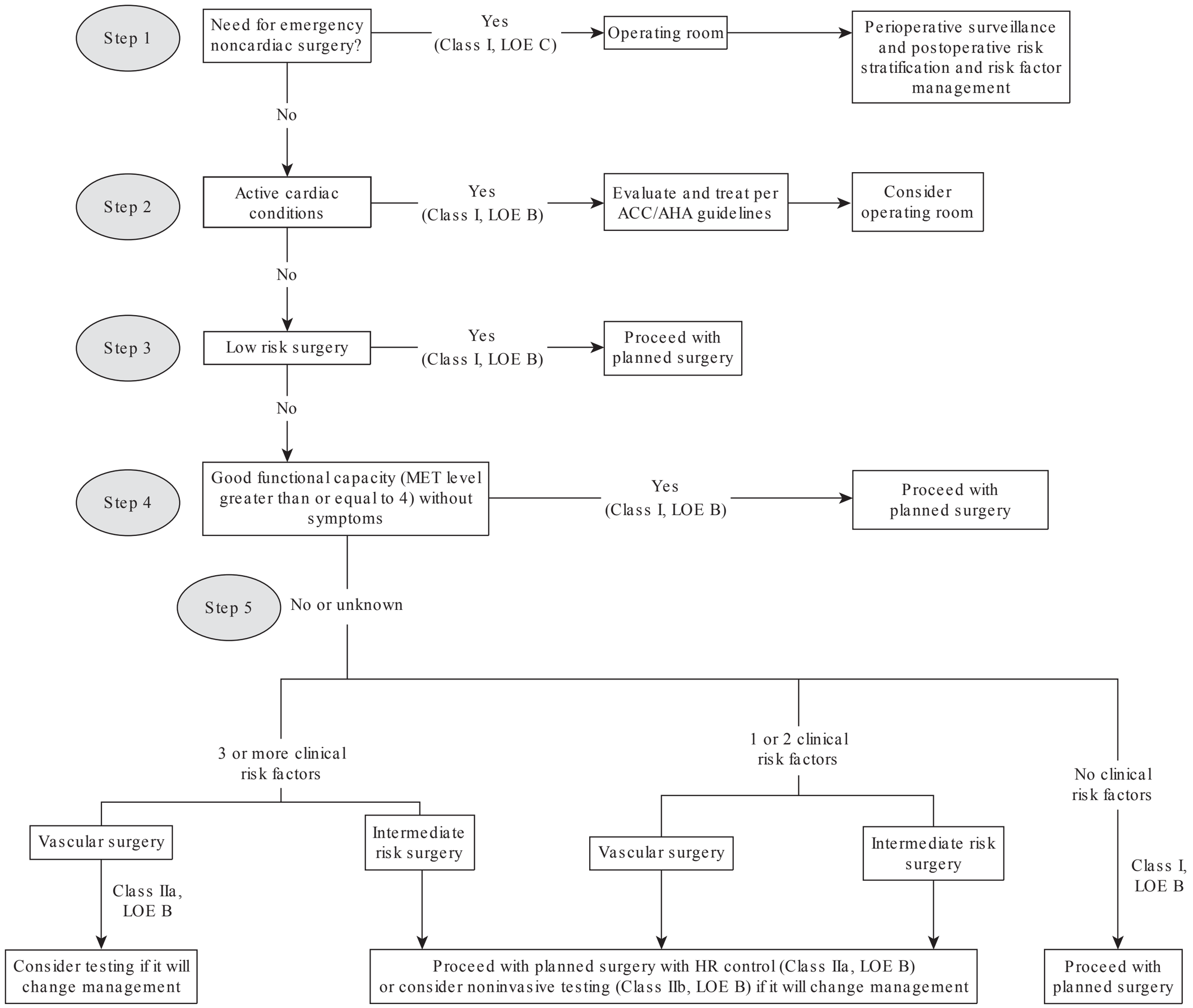

FIGURE 149.2. Cardiac evaluation and care algorithm for noncardiac surgery based on active conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or older. (Reprinted from Fleisher et al: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary. *J Am Coll Cardiol* 50(17):1716, 2007, with permission from Elsevier.)

preanesthetic evaluation [36]. The task force cited that few screening ECG findings resulted in changes in clinical management. They also stated that based on evidence, age alone may not be an indication for ECG. Proponents of screening ECGs argue that these studies may identify patients with coronary disease not recognized by clinical history. Moreover, these newly identified patients could then be further tested or medically managed with beta-blockade. However, this argument may be flawed for several reasons. First of all, a positive ECG in an asymptomatic patient would not alter further testing if the practitioner uses the ACC/AHA algorithm [30]. Second, according to van Klei et al., ECG abnormalities, including left and right bundle branch blocks, were no more predictive of postoperative MI than history alone [37]. Finally, starting beta-blocker therapy is probably not indicated in otherwise asymptomatic patients [30]. Fleisher, however, does make one argument that may be valid for obtaining preoperative ECG [38]. Without a preoperative ECG, the first occasion that the ECG may be seen as abnormal is when the patient is in the operating room prior to induction. Under these circumstances, it may be beneficial to compare the new findings with an old ECG to identify the acuity of the changes and determine whether or not to proceed. Currently, however, the ACC/AHA states that preoperative screening ECGs are indicated only for vascular surgeries and for certain patient populations having intermediate-risk surgery (Table 149.5) [30].

PREOPERATIVE NONINVASIVE CARDIAC TESTING

As mentioned earlier, part of the ACC/AHA guidelines [29] was to help direct the clinician as to which patients should undergo preoperative testing. The guidelines, however, did not elucidate which noninvasive testing regimen should be undertaken. Exactly which method of evaluation is chosen is again another source of controversy. Testing the low-risk patient undergoing low-risk surgery is ultimately an exercise in futility and an overall waste of time and resources. High-risk patients undergoing high-risk surgery will most likely benefit from invasive testing [39]. The question arises as to what to do with the patient

TABLE 149.5

INDICATIONS FOR PREOPERATIVE RESTING ECG

Benefit >>> Risk (class I)
1. Patients with at least one clinical risk factor (coronary heart disease, history of CVA, renal insufficiency, diabetes mellitus) who are undergoing vascular surgery
2. Patients with known coronary heart disease, peripheral arterial disease, or cerebrovascular disease who are undergoing intermediate-risk surgery

Benefit >> Risk (class IIa)
1. Patients with no clinical risk factors who are undergoing vascular surgery

Benefit ≥ Risk (class IIb)
1. Patients with at least one clinical risk factor who are undergoing intermediate-risk surgery

Risk > Benefit (class III)
1. Asymptomatic patients undergoing low-risk surgery

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with intermediate clinical predictors and needs intermediate- to high-risk surgery [40].

The purpose of noninvasive testing is to accrue information that adds to that already provided by whichever cardiac risk index was implemented. Ideally, it will not lead to harmful delays but rather to proven therapy to reduce risk [3].

There are some generally accepted principles regarding what exactly is an effective screening test [36]. These principles should be kept in mind when assessing any test:

1. Accuracy of test: The test must be able to detect the target condition earlier than without screening and with sufficient accuracy to avoid producing large numbers of false–positive and false–negative results.
2. Effectiveness of early detection: Screening for and testing persons who have early disease should improve the likelihood of favorable health outcomes (e.g., reduced disease-specific morbidity and mortality) compared to treating patients when they present with signs and symptoms of the disease.

Exercise Stress Testing

Exercise stress testing is a well-established mechanism of assessment that allows the identification or absence of myocardial ischemia while the patient is undergoing physical exertion. The purpose of the examination is to elevate the myocardial oxygen consumption to a rate in which demand outweighs supply, leading to ischemic changes on ECG. The inherent drawback of this method of assessment is that it relies on patient participation. At times, due to deconditioning or medical issues, such as claudication, the patient cannot reach target heart rate and thus ischemic episodes may be missed.

Unfortunately in meta-analysis, the mean sensitivity of exercise ECG testing for the prediction of multivessel coronary artery disease has been reported to be 81% (range 40% to 100%) with a mean specificity of 66% (range 17% to 100%) [41]. The meta-analysis also reconfirmed that the sensitivity of the examination was adversely affected in patients who could not reach maximal heart rate, especially vascular surgery patients in which approximately 50% could not reach the target rate.

In addition to the failure to reach target heart rate, other limitations of exercise testing exist. These include ECG changes on resting ECG, the presence of left bundle branch block, failure in determining the extent of myocardial ischemia, and lack of information regarding left ventricular function [42].

Myocardial Perfusion Imaging

To overcome some of the inherent problems of exercise stress testing, pharmacologic stress myocardial perfusion imaging was developed [43]. This examination consists of the administration of a vasodilating agent such as adenosine or dipyridamole to induce vasodilation that would parallel the effect of exercise on coronary anatomy. In addition, a radionuclide is administered, such as thallium-201. Images are obtained over time and positive examinations are those in which areas of initial filling defects resolve, or undergo redistribution of thallium, during the rest phase.

Several complications and contraindications exist with the use of adenosine and dipyridamole. Since they are potent vasodilators, these agents are obviously contraindicated in those patients with preexisting hypotension and ongoing symptoms of unstable angina. Other relative contraindications to administration of adenosine include high-degree atrioventricular block, bronchospastic disease, and atrial arrhythmia disorders such as sick sinus syndrome.

Eagle et al. found that patients with one or two risk factors for coronary artery disease, and redistribution on dipyridamole thallium had a 29% cardiac event rate versus a 3.2% rate in patients without redistribution. The sensitivity of the examination, however, appears to be in detecting the presence or absence or coronary artery disease, not ischemia [23].

In addition it has been reported that the accuracy and positive likelihood ratio for dipyridamole thallium stress testing is low and that the examination does not provide independent prognostic value beyond clinical risk stratification [44]. Other prospective blinded studies confirmed a lack of association between reversible defects on dipyridamole thallium and adverse cardiac events in patients undergoing elective vascular surgery (of note, these studies excluded low-risk patients undergoing vascular surgery) [45,46].

In the study by de Virgilio et al. [46], the adverse cardiac event rate was 13.8% for patients with a reversible defect on thallium testing versus 9.8% for those who did not have a reversible defect ($p = 0.70$). The adverse event rate in patients with two or more reversible defects was 12.5% versus 11.1% in patients with fewer than two reversible defects. Sensitivity with two or more defects was 11%, with a specificity of 90%. The overall positive and negative predictive values were 12.5% and 89%, respectively. The authors concluded that since there was no demonstrable correlation between dipyridamole thallium and perioperative adverse cardiac events, one could not recommend the test as a screening tool prior to vascular surgery.

Another imaging study is dipyridamole technetium-99m sestamibi testing. Technetium-99m sestamibi is a radiotracer that differs from thallium-201 and ultimately allows for acquisition of higher resolution tomographic cardiac images. Stratmann et al. [47] studied 229 patients scheduled for vascular surgery who underwent sestamibi testing. Of those enrolled, 197 underwent surgery within 3 months of the initial examination with an overall cardiac event rate of 5%. The perioperative cardiac event rate between those with normal, abnormal, or reversible sestamibi images was not clinically significant; however, abnormal and reversible sestamibi images were independent multivariable predictors of increased risk of late cardiac events.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography (DSE) was developed as a tool for assessing the presence of coronary artery disease and

was reported by Berthe et al. [48] in 1986. Essentially the examination is composed of the administration of a pharmacologic inotropic agent (e.g., dobutamine), which is designed to increase heart rate and myocardial contractility, thus increasing myocardial oxygen consumption. In the presence of coronary artery disease, demand will overcome supply and myocardial dysfunction will be present. Myocardial dysfunction will be evident by echocardiography, manifested by areas of hypokinesis, akinesis, or dyskinesis. The development of new wall motion abnormalities following dobutamine administration is considered an indication of significant coronary artery disease [49].

When dobutamine stress echocardiography and dipyridamole-thallium testing were compared in the same patient population, they appeared to have comparable specificity and sensitivity [50]. A subsequence meta-analysis study revealed a 9% incidence of perioperative myocardial infarction in patients with reversible ischemia or regional wall abnormalities in one or more areas [51].

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) Study Group performed a large retrospective study with results released in 2001. The study noted that the adverse event rate was 10.6% in patients with three or more cardiac risk factors and five or more segments of new wall motion abnormalities (NWMAs) versus a 2% adverse event rate in patients without NWMAs. It is also interesting to note that the study reported perioperative death and myocardial infarction rates of 6.5%, 10%, and 16% in patients with respective scores on a modified Revised Cardiac Index of 3, 4, and 5 who were treated with beta-blockade but also had ischemia on DSE [52]. A drawback to the utilization of echocardiography was that the study showed that DSE did not add incremental value in low- or medium-risk patients (score of 0 to 2 on Revised Cardiac Risk Index) [3].

Although the results of this retrospective study were encouraging, there are other studies that tend to question the validity of DSE for preoperative evaluation. It appears that echocardiography has limited prognostic value as a routine test. Rohde et al. [53] reported that an abnormal echocardiogram with any degree of systolic dysfunction, moderate to severe left ventricle hypertrophy, moderate to severe mitral regurgitation, or aortic gradient of 20 mm Hg or higher provided a sensitivity of 80%, specificity of 52%, positive predictive value of 12%, and negative predictive value of 97%. However, severe left ventricular (LV) dysfunction compared to mild–moderate LV dysfunction did not have a strong association with cardiogenic pulmonary edema and MI. Thus, given the heterogeneity of findings, it appears that echocardiography adds little to risk models.

Another retrospective study in 2002 by Morgan et al. [54] examined the utility of dobutamine stress echocardiography in 85 preoperative patients in accordance with the ACC/AHA guidelines. The DSE was positive in 4 patients (4.7%), negative in 74 (87.1%), and nondiagnostic in 7 (8.2%). The DSE obtained in 48 patients with a history of diabetes mellitus (DM), mild angina, or "minor clinical predictors" produced only negative results. Of the four positive patients, three underwent angiography and one underwent coronary artery bypass grafting (CABG) prior to surgery. No patient had any perioperative morbidity related to myocardial ischemia. Morgan et al. [54] went further to recommend that DSE is recommended in patients with:

1. Intermediate clinical predictors (one or more) [prior MI, compensated CHF, DM with mild angina] with poor functional capacity less than 4 METs
2. Intermediate clinical predictors (one or more) with moderate to excellent functional capacity greater than 4 METs and high surgical risk and unable to perform exercise stress test

Grayburn and Hillis [3] went on to state more strongly that the test had limited value given that the likelihood ratio of a positive test report was low and thus had a low positive predictive value. The authors strongly felt that patients with positive test results are often subjected to further evaluation that may cause an unnecessary delay in noncardiac surgery.

A recent study by Kertai et al. [55] used a meta-analytic approach adjusting for reported variability in test performance between the individual studies. The results revealed that there was clinical utility for the use of dobutamine stress echo in perioperative risk assessment. Overall sensitivity and specificity of the test were found to be high, 85% and 70%, respectively. The conclusion by the authors was that the predictive value of a positive DSE for the composite endpoint of cardiac death and myocardial infarction was significantly increased. However, much work is still in progress regarding the overall utility of DSE and cardiac risk assessment.

So is DSE better than nuclear scintigraphy (thallium imaging)? Beattie et al. [56] addressed this question with a recent meta-analysis. The authors felt that the meta-analysis contained the statistical power to demonstrate that DSE had better negative predictive characteristics than thallium imaging (TI). Although a moderate to large perfusion defect by either DSE or TI predicted postoperative MI and death, they concluded that DSE was superior to TI in predicting postoperative cardiac events.

What about the patient with a negative examination? The meta-analysis [56] also revealed that a negative DSE reduced the probability of MI or death. It was evident that there were fewer false negative DSE results. And what about the patient with moderate or multiple defects? Moderate or multiple defects on DSE were noted to be at least as accurate as the demonstration of a large perfusion defect on TI. However, the group's final conclusion was that a negative test did not reliably confirm less risk of a perioperative cardiac event, although a positive DSE was two times more predictive than a positive TI.

Invasive Cardiac Evaluation

Once a decision has been made regarding preoperative invasive cardiac evaluation, either based on clinical history or noninvasive testing, several questions remain. Namely, what is to be done with the information obtained? Is a surgical or percutaneous intervention warranted? Will it make a difference?

There are clearly some indications in which invasive testing are warranted. These include recent myocardial infarction with residual angina, angina unresponsive to medical therapy, unstable angina, and proposed intermediate-risk or high-risk noncardiac surgery after equivocal noninvasive test results [39].

Essentially, the original ACC/AHA guidelines [29] did not recommend coronary angiography as risk stratification in patients undergoing noncardiac surgery; however, they did recommend angiography if indications for angiography independent of planned surgery were present [40]. However, confusion persists regarding the role of preoperative angiography and subsequent preoperative intervention to reduce risk of noncardiac surgery.

Role of Coronary Artery Bypass Grafting Prior to Noncardiac Surgery

In the 1980s, an initial study by Hertzer et al. [57] revealed that the cumulative cardiac mortality rate at 10 years was markedly increased for patients with suspected but uncorrected coronary artery disease as compared with those patients without evidence of coronary artery disease or those patients who had

undergone myocardial revascularization. This ultimately led to the belief that aggressive coronary revascularizations prior to vascular operations were warranted.

A series of studies by Gagnon et al. [58] and Allen et al. [59] also recommended prophylactic CABG or angioplasty prior to noncardiac surgery. Nielsen et al. [60] found in the early 1990s that patients who had a CABG operation appeared to have a low rate of perioperative cardiac complications. This observation was further enhanced by Eagle et al. [61] who used the Coronary Artery Surgery Study (CASS) registry. After reviewing the data, the group found that patients who underwent major vascular, abdominal, thoracic, or head/neck surgery after previous CABG had fewer perioperative deaths and myocardial infarctions than patients receiving medical therapy.

Ultimately, these observational studies became the basis for the ACC/AHA guideline recommendations that invasive testing for risk stratification was not indicated in patients who had a CABG surgery within 5 years and were currently without symptoms [29]. Grayburn and Hillis [3] have strongly voiced opposition to the utilization of CABG in the *asymptomatic* patient. They felt that the morbidity and mortality associated with the CABG procedure, which includes nonfatal MI, death, stroke, and cognitive dysfunction, outweighed any benefit.

The group also held the valid viewpoint that recovery from CABG would cause a significant delay in obtaining the noncardiac surgery. In fact, as indicated by Mason et al. [62], coronary angiography appears to carry a 0.3% risk of mortality, while CABG has been reported to have an operative risk of 3% overall and approximately 5% in the patient with peripheral vascular disease.

One of the stronger studies in support of avoiding coronary artery revascularization before noncardiac surgery was published from the CARP (Coronary Artery Revascularization Prophylaxis) trial [63]. This was a multicenter trial that randomly assigned patients who were at increased risk and had clinically significant coronary artery disease to either undergo revascularization or no revascularization before elective major vascular surgery. The major end point of the study was long-term mortality. A group of 510 patients out of 5,859 were deemed eligible, with 258 assigned to preoperative revascularization (CABG or percutaneous angioplasty) and 240 assigned to medical management.

The study revealed that at 2.7 years, mortality in the revascularization group was 22% and in the nonrevascularization group 23%. Positive postoperative myocardial infarction (as documented by elevated troponin levels) was 12% in revascularization group and 14% in nonrevascularization group. One problem with the study was that it lacked the power to detect a beneficial effect on the intervention in the short term; however, the group felt that there appeared to be no reduction in the number of postoperative myocardial infarctions, deaths, or days in the hospital. Another criticism of the study has been that the selection of patients was based on intermediate or minor clinical predictors and as such may have selected a lower risk patient population. The study also did not account for patients with left main disease, aortic stenosis, or severe left ventricular dysfunction [64].

A recent review of the role of preoperative coronary revascularization was performed by Kertai [65]. Within the review, Kertai noted that though CABG provided more complete revascularization as compared to percutaneous coronary intervention, the CARP trial and subsequent studies with subgroup analyses found that coronary revascularization preoperatively did not improve perioperative and long-term mortality rates.

The Role of Preoperative Coronary Angioplasty

As evident from the previous section there appears to be little support for prophylactic CABG in the asymptomatic patient presenting for noncardiac surgery. However, what about the patient who has received a percutaneous coronary intervention (PCI)? Does preoperative PCI reduce the operative risk of the patient undergoing noncardiac surgery?

Several studies have addressed this question. In a retrospective cohort study by Posner et al. [66], adverse outcomes after noncardiac surgery among patients with a prior PCI, patients with nonrevascularized coronary artery disease (CAD), and normal controls were compared. They ultimately compared the risk for developing adverse cardiac outcomes within 30 days (notably death, myocardial infarction, angina, CHF, malignant dysrhythmias, cardiogenic shock, coronary artery bypass graft after angioplasty). The results of the study revealed that patients who underwent PCI had twice the risk of adverse cardiac outcome as normal controls and half the risk of adverse outcomes as patients with CAD. Compared to the group with uncorrected CAD, the PCI group exhibited no difference in myocardial infarction rates or death.

Timing between the PCI and noncardiac surgery was also important in this study. It was revealed that patients who had a PCI more than 90 days from the noncardiac surgery seemed to have a lower risk of poor outcome as compared to the nonrevascularized patients with CAD. But of note, the study revealed that those who underwent recent PCI had a threefold increase in risk compared to normal controls.

Posner et al. felt that the most surprising result of the study was the similarity of outcome between patients with recent PCI and uncorrected CAD. The group also felt that this helped to substantiate earlier work by Lauperta et al. [67] and Seeger et al. [68] who found similar noncardiac surgery outcomes between patients who underwent prophylactic revascularization and patients without intervention.

Adding to the controversy is a retrospective study performed by Landesberg et al. [69] who reviewed patients who underwent coronary revascularization prior to noncardiac surgery based on the results of a preoperative positive stress thallium examination. His group concluded that long-term survival after major vascular surgery was significantly improved in patients undergoing coronary revascularization. However, Godet et al. [70] were highly critical of this provocative study, deeming it importantly flawed on several points:

1. The study lacked adequate power.
2. Propensity score analysis, which balances all the observed covariants associated with exposure to PCI [71], did not take into account important variables occurring during or after the procedure that may be associated with poor outcomes.
3. The goodness of fit of the propensity score was significant, indicating inappropriate fit of the model.

Godet et al. ultimately performed their own study that analyzed a cohort of 1,152 patients after abdominal aortic aneurysm repair, in which 78 underwent PCI. The study revealed five variables that independently predicted severe postoperative coronary events: age over 75 years, blood transfusion, repeated surgery, preoperative hemodialysis, and previous cardiac failure. The study also revealed five variables that independently predicted postoperative death: age over 75 years, repeated surgery, previously abnormal ST segment/T waves, previous hypertension, and previous cardiac failure. In their conclusions, the group stated that in the PCI group, the observed percentages of patients with a severe postoperative coronary event (9%) were not significantly different from the expected percentages (8.2% and 6.9%, respectively). Of note, when all patients were pooled together, the odds ratios of PCI were not significant and the propensity score analysis provided a similar conclusion.

In the Bypass Angioplasty Revascularization Investigation (BARI) trial, a prospective, randomized trial was designed to

compare PCI to CABG on risks of subsequent noncardiac surgery [72]. The results ultimately indicated that the rates of myocardial infarction and death between the two groups PCI and CABG after noncardiac surgery were similar, thus failing to favor one intervention versus another.

In 2007 the COURAGE trial research group reported the results of a multicenter, randomized trial of 2287 patients with multivessel coronary artery disease. The study noted that PCI compared with optimal medical therapy did not reduce the risk of death, myocardial infarction, or other major cardiovascular events during an average observation period of 4.6 years [73]. Though this study was not directed to the patient undergoing noncardiac surgery, it makes the point that interventions in medically optimized, cardiac stable patients may have little value in reducing overall morbidity and mortality.

Obviously, the question regarding the value of PCI or coronary bypass grafting prior to major vascular surgery has not been definitively answered. Complicating the situation is the observation that both the risk of surgery and PCI are substantially higher in patients with peripheral artery disease. This, as noted by Saw et al. [74], may be due to systemic atherosclerotic burden that ultimately leads to increased cardiovascular and cerebrovascular complications.

Considerations for the Patient with Recent Percutaneous Coronary Intervention

An important clinical situation to consider is what to do with the patient who has undergone recent PCI. It is conceivable that during the noninvasive preoperative screening of the intermediate- to high-risk patient, a clinically significant coronary artery lesion is noted. The decision to correct the lesion is usually undertaken by the invasive cardiologist, sometimes during a diagnostic angiography [75]. Balloon angioplasty has given way to more definite treatments such as the placement of bare metal or drug-eluting coronary artery stents. Exactly when and which intervention was made has tremendous implication if these patients present for noncardiac surgery.

Complications from stent placement usually arise from the nature of the thrombogenicity of the stent at the blood-tissue interface leading to thrombosis or embolization. There appear to be multifactorial causes for these events, namely, the type of stent, its length, the size of the final lumen diameter, and the presence of persistent dissection at the time of implantation. Cutlip et al. [76] have reported a 50% incidence of acute myocardial infarction that carries an overall 20% mortality rate in the patient who has had thrombosis with recent stent placement. These concerns have also caused many to recommend caution when dealing with patients and recent PCI [77].

The 2002 ACC/AHA recommendations regarding the patient who has a coronary artery stent suggested at least 2 weeks and ideally 4 to 6 weeks between stent implantation and noncardiac surgery [29]. This would include a full 4 weeks of dual antiplatelet therapy (aspirin and a thienopyridine, such as clopidogrel or ticlopidine) during stent reendothelialization and 2 weeks for restoration of normal platelet function.

Interestingly, the recommendations by the 2002 ACC/AHA committee arose not from randomized controlled trials, but from two retrospective studies [29]. Kaluza et al. [78] noticed that 40 patients who underwent noncardiac surgery within 2 weeks of implantation had a high incidence of severe, catastrophic complications. Of the patients evaluated, 18% had myocardial infarctions, 20% died, and 28% had major bleeding. In a larger series, Wilson et al. [79] noted that 4% of patients undergoing noncardiac surgery within 6 weeks of stent placement suffered a myocardial infarction in which 2.9% of this group ultimately died. They noted that there were no complications seen in patients who were 7 weeks after implantation.

A retrospective study reviewing the risks of noncardiac surgery after coronary stenting was performed by Reddy and Vaitkus [80]. In their small patient population, they noted that of the patients who had major adverse cardiovascular events (MI, stent thrombosis, major bleeding, or death), 38% had undergone noncardiac surgery within 14 days of stent placement and 62% had undergone noncardiac surgery 15 to 42 days after implantation. No patient developed major adverse cardiovascular events after 42 days, leading the authors to suggest that a patient should be considered high-risk if surgery was performed up to 6 weeks following stent placement.

Drug-Eluting Cardiac Stents

It is also important to note that the 2002 ACC/AHA guidelines [29] were only for bare metal stents and not for drug-eluting coronary stents or patients who are under brachytherapy. The presence of paclitaxel or sirolimus may delay endothelialization of the coronary stent and may necessitate a longer period of antiplatelet therapy [81]. A case report by Auer et al. [82] discusses a patient who had the simultaneous placement of a bare metal stent in the right coronary artery and two paclitaxel-eluting stents in the left circumflex 12 weeks prior to noncardiac surgery. Interestingly, 2 hours after surgery the patient had an acute myocardial infarction and catheterization revealed patency of only the RCA-bare metal stent.

In an editorial, Berger et al. [83] recommended that if a patient was scheduled to have noncardiac surgery within 2 months of PCI and the surgery/surgeon did not permit continuation of aspirin and clopidogrel throughout the perioperative period, then bare-metal stents should be used. Mendoza et al. [84] recommended at least a 3-month delay from time of implantation of a drug-eluting stent and noncardiac surgery. This recommendation was based on observations and extrapolation of case reports.

However, a new set of recommendations has been issued regarding the discontinuation of antiplatelet therapy in patients with coronary artery stents. The American Heart Association Scientific Statement by the AHA/ACC/ACS/ADA in February 2007 stated that elective surgical procedures in patients receiving drug-eluting stents should be delayed for at least 12 months. During that time, the patient should receive an entire course of dual antiplatelet therapy composed of aspirin and thienopyridines. However, if surgery cannot be delayed, then the consensus of the group was to recommend the implantation of bare metal stents or balloon angioplasty or continuation of aspirin throughout the perioperative period [85]. This recommendation was also incorporated into the 2007 ACC/AHA guidelines [30]. A summary of the recommendations regarding percutaneous coronary interventions is noted in Figure 149.3.

Heart Failure and Noncardiac Surgery

Definition

As mentioned earlier, one of the high-risk clinical predictors for a postoperative complication is the history of heart failure (HF). The question arises as to how to approach the patient with a history of HF and how best to manage these patients as they present for noncardiac surgery. In 2003, the Framingham Heart Study estimated that there are approximately 550,000 new cases of HF each year with a prevalence of 5 million patients [86].

Heart failure patients presenting for noncardiac surgery are known to have a twofold higher mortality and readmission rate than those patients with CAD alone or no disease. This has been noted to be the case across all types of surgeries. In

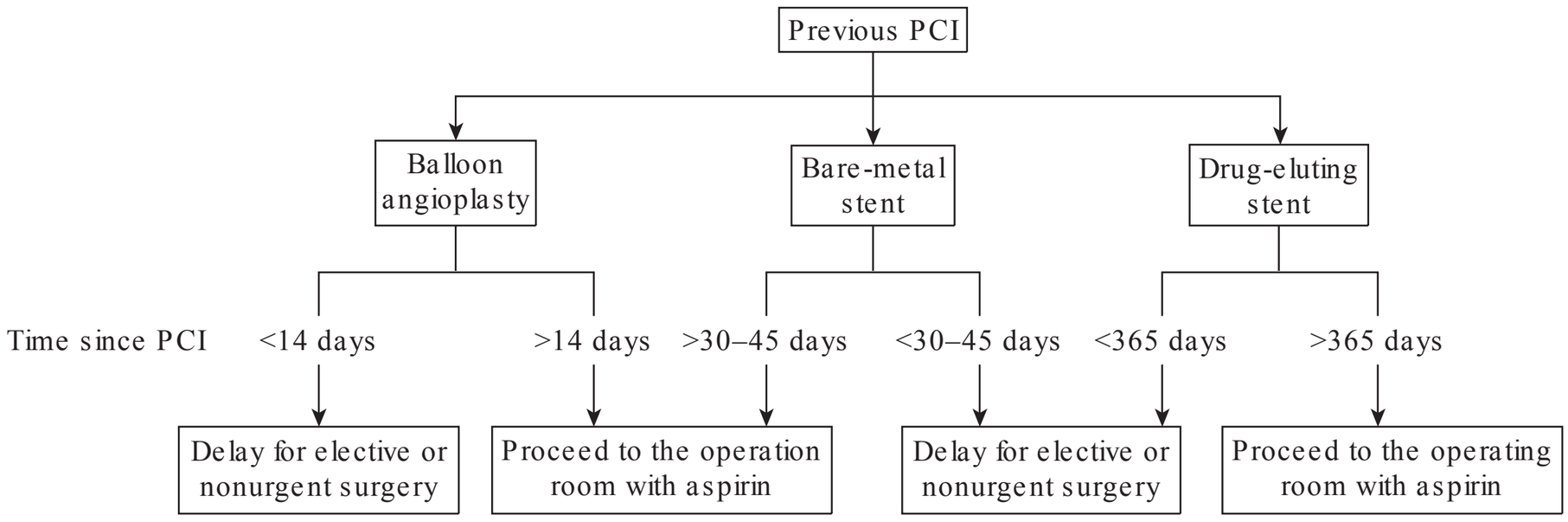

FIGURE 149.3. Proposed approach to the management of patients with previous percutaneous coronary intervention who require noncardiac surgery, based on expert opinion. (Reprinted from Fleisher et al: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary. *J Am Coll Cardiol* 50(17):1720, 2007, with permission from Elsevier.)

fact, there is a two- to fourfold increase in mortality for HF patients compared with all others [87]. In evaluating outcomes of Medicare HF patients undergoing noncardiac surgery, Hernandez et al. [88] used a multivariable logistic regression model to assess mortality and readmission rates in the presence of preexisting HF. The group noted that the risk-adjusted operative mortality (defined as death before discharge or within 30 days of surgery) was 11.7% in the HF group versus 6.2% in the control group and 6.6% in the group with isolated CAD. The risk-adjusted 30-day readmission rate in the HF group was as high as 20% and with control, it was approximately 11%. The patients with CAD without the presence of HF had a readmission rate of 14.2%.

Defining exactly which signs and symptoms constitute CHF can be somewhat controversial. However, the ACC/AHA have developed a definition of heart failure that includes various stages, each with their own specific treatment regimen (Table 149.6). It is also important to remember that patients with left ventricular dysfunction may present with a variety of syndromes, notably, a syndrome of decreased exercise tolerance, a syndrome of fluid retention, or those who have no symptoms and incidentally discovered left ventricular dysfunction [89].

TABLE 149.6

ACC/AHA STAGES OF EVOLUTION HEART FAILURE

Stage A: High risk for heart failure, but without structural heart disease or symptoms of heart failure (e.g., hypertension, coronary artery disease, diabetes mellitus, utilizing cardiotoxins, or family history of cardiomyopathy)
Stage B: Structural heart disease but without symptoms of heart failure (e.g., patients with previous MI, LV systolic dysfunction, asymptomatic valvular disease)
Stage C: Structural heart disease with prior or current symptoms of heart failure (e.g., patients with known structural heart disease, shortness of breath and fatigue, reduced exercise tolerance)
Stage D: Refractory heart failure requiring specialized interventions (e.g., patients who have marked symptoms at rest despite maximal medical therapy)

LV, left ventricular; MI, myocardial infarction.
From Hunt SA, Baker DW, Chin MH, et al: ACC/AHA Guidelines for the evaluation and management of congestive heart failure in the adult: executive summary. *Circulation* 104:2996–3007, 2001, with permission.

Evaluation of the Patient with Heart Failure

The Lee Revised Cardiac Risk Index does not take into account changes in the patient's clinical status over time. Hernandez et al. [90] gives the following example of a common clinical conundrum. For example, if a patient has decompensated HF on the day of surgery, the surgery is subsequently cancelled for the patient to clinically improve. We can assume that improvement has been made over time and the patient presents again for noncardiac surgery. The patient's calculated risk remains the same, which may or may not reflect reality. This situation is similar to the patient who has a recent acute coronary syndrome who returns for surgery after being delayed for months to undergo coronary revascularization.

Are there specific noninvasive tests that have particular value when assessing the patient with CHF presenting for noncardiac surgery? Numerous studies have shown value in diagnostic and prognostic markers of HF such as natriuretic peptides. With commercial assays of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide being more widespread, it may be possible to improve both the preoperative classification of HF and diagnosis of HF as a postoperative complication by incorporating markers in routine assessment [90–92].

Echocardiography has been found to have a limited prognostic value as a routine test in the presence of heart failure. Rohde et al. [53] addressed this issue regarding the value of transthoracic echocardiography as a tool for risk stratification and found that an abnormal echocardiogram with any degree of systolic dysfunction, moderate to severe left ventricle hypertrophy, moderate to severe mitral regurgitation, or aortic gradient of 20 mm Hg or higher provided a sensitivity of 80%, specificity of 52%, a positive predictive value of 12%, and negative predictive value of 97%. However, severe LV dysfunction compared to mild to moderate LV dysfunction did not have a strong association with cardiogenic pulmonary edema and MI. Because of the heterogeneity of findings, the authors concluded that transthoracic echocardiography added little to risk models.

Right Heart Catheterizations in the Heart Failure Patient

The utilization of right heart catheterization (RHC) in patients having noncardiac surgery has also been evaluated. Obviously, intraoperative hemodynamic changes are associated with increased perioperative complication rates [10]. However, in a

TABLE 149.7

TESTS AND STRATEGIES FOR MANAGING PATIENTS WITH HEART FAILURE IN THE PERIOPERATIVE SETTING

Perioperative beta-blockade: Patients with HF should normally be taking beta-blockers for long-term benefits. If not, try to start beta-blocker therapy early enough to ensure it is well tolerated before surgery.
Stress testing: It should be done in high-risk patients with ≥3 points on the Revised Cardiac Risk Index or in patients considered at intermediate risk who are unable to receive perioperative beta-blockers of if testing would be done as normal clinical care for long-term goals.
Degree of HF compensation: Currently requires clinical judgment. No objective testing strategies have been evaluated in the perioperative setting.
Echocardiography: Routine use of echocardiography does not add information for risk stratification or potential changes in management. It should be reserved for evaluation of clinical changes as done for routine management of HF.
Right heart catheterization and monitoring: Current evidence does not support its routine use. If needed, measurement of central venous pressure is adequate for perioperative management of volume status.

HF, heart failure.
Adapted from Hernandez AF, Newby LK, O'Connor CM: Preoperative evaluation for major noncardiac surgery—focusing on heart failure. *Arch Intern Med* 164:1729–1736, 2004.

recent randomized controlled trial of elderly patients undergoing major noncardiac surgery, Sandham et al. [93] showed no benefit for the utilization of perioperative RHC. Within the study, 2,000 patients over the age of 60 with ASA classifications of III and IV were randomized to RHC-directed care versus usual care. Results revealed no improvement in the perioperative course of the RHC-directed therapy over those receiving standard care. There was a slightly higher incidence of pulmonary embolism in the catheter group that was not explained. A reported limitation of this study was that the patients with a NYHA class III or IV HF comprised only 13% of study population. Thus, it is clearly unknown whether RHC is of value in this subpopulation. The study also noted that there was a higher use of inotropes (48.9% vs. 32.8%) in the RHC-directed group, which the authors felt may be the reason for the overall lack of benefit of the invasive monitors.

The appropriate management for this patient population includes risk assessment by the previously mentioned tools. This goes along with constant surveillance and reevaluation of clinical scenarios as they arise. Hernandez et al. [90] suggested a template for tests and strategies for the management of patients with heart failure in the perioperative period (Table 149.7). Again, tailoring to each specific patient is warranted.

Pharmacologic Interventions to Reduce Risk During Noncardiac Surgery

It is obvious that many patients with coronary artery disease will continue to present for noncardiac surgery. Interventions such as coronary stent placement and CABG appear to be of value only if the patient is symptomatic prior to coming for surgery. As such, there is a strong interest in developing pharmacologic regimens that may help reduce the incidence of major cardiac events.

Role of α_2-Agonists and Myocardial Ischemia Prevention

The purported mechanism of action for α_2-agonists in the prevention of myocardial ischemia is a reduction in sympathetic outflow and ultimately myocardial oxygen consumption. The α_2-agonists are known to reduce postganglionic norepinephrine availability and spinal efferent sympathetic output. In the European Mivazerol trial, a double-blind, randomized placebo controlled study was performed at 61 European centers utilizing intravenous mivazerol, an α_2-agonist [94]. Patients either had documented coronary artery disease or were at high-risk for the disease. The drug was administered for 72 hours from induction of anesthesia into the postoperative period. There was a mix of perceived high-risk or intermediate-risk surgeries including vascular surgery or nonvascular thoracic, abdominal, and orthopedic procedures. The conclusions of the study revealed no alterations in the rates of myocardial infarction or cardiac death in patients with known disease.

Two further studies seemed to substantiate the protective properties of α_2-agonists, specifically clonidine. Maekawa et al. [95], in a meta-analysis of the literature, noted that in subgroup analysis, clonidine reduced the incidence of myocardial ischemia in patients undergoing cardiac or noncardiac surgery. Rates of bradycardia were similar in the clonidine and the placebo groups. Wallace et al. [96] performed a prospective, double-blind, clinical trial with patients with documented coronary artery disease or who were at-risk for coronary artery disease. Oral clonidine plus patch therapy was used, and patch therapy was maintained for 4 days. There was a noted decrease in the incidence of perioperative myocardial ischemia with clonidine, intraoperatively and postoperatively. Also of interest, there was a marked reduction in the incidence of postoperative mortality for up to 2 years.

In a quantitative systematic review, six trials utilizing α_2-agonists were reviewed [97]. The group noted that α_2-agonists decreased the incidence of myocardial ischemia during surgery (19.4% vs. 32.8%) compared with placebo. Of note, there was not a significant decrease in myocardial infarction rates (6.1% vs. 7.3%) compared with placebo. Also of significance, the α_2-agonist decreased the risk of cardiac death from 2.3% to 1.1% as compared to placebo.

Statin Therapy

Statins have recently gained favor as medications used to possibly alter perioperative myocardial ischemia. These low-density lipoprotein lowering agents are well known to attenuate coronary artery plaque inflammation. Statins also contain pleiotropic properties that possibly affect plaque stability by the inhibition of anti-thrombogenic, antiproliferative, and leukocyte anti-adhesive properties [98] (Table 149.8).

Early work has shown a decrease in risk of a major coronary event in the presence of statin therapy [99]. In a relatively recent case–control study, Poldermans et al. [104,105] have shown that the utilization of statin therapy has been associated with a fourfold reduced risk in perioperative mortality. This result was seen consistently within subgroups according to the type of surgery, cardiac risk factors, and cardioprotective medication use including aspirin and beta-blockers. These results were also later substantiated in a randomized trial by Durazzo et al. [106], which also noted a reduction in perioperative myocardial infarction rates.

TABLE 149.8

PROPOSED MECHANISM OF STATINS IN THE PRESENCE OF CORONARY ARTERY DISEASE

Inhibition of neovascularization [99–101]
Inflammatory modulation [99–101]
↑ Atherosclerotic plaque stabilization by decreasing the size of the lipid core [101]
↓ Endothelial basement membrane degradation [101]
↓ Smooth muscle apoptosis by decreasing macrophage infiltration [100,102]
↓ The release of matrix metalloproteinases [100,102]
↓ Interferon-Γ release and leukocyte adhesion [100–102]
↓ Complement mediated injury by decreasing C-reactive protein [100–103]
↑ Decay-accelerating factor [100]
↑ The expression of the vasodilator eNOS and ↓ the vasoconstrictor endothelin-1 [100,101]
↓ Thrombogenic response to plaque rupture by inhibiting platelet activation (by increasing eNOS and decreasing thromboxane A2 production) [100,102]

eNOS, endothelial nitric oxide synthetase.
Adapted from Biccard BM, Sear JW, Foex P: Statin therapy: a potential useful perioperative intervention in patients with cardiovascular disease. *Anaesthesia* 60:1106–1114, 2005.

In a review of the literature by Biccard et al. [107], it was evident that a majority of studies have shown statins to be beneficial in the surgical patient, especially in regard to all-cause mortality, cardiovascular mortality, and myocardial infarction. The group ultimately recommended that statins be administered preoperatively in high-risk patient populations, but recognized the fact that larger studies would need to be performed to verify this position.

Assuming patients present for noncardiac surgery while on statin drugs, is it acceptable to discontinue therapy? Lindenauer et al. [108] noted that temporarily discontinuing statin therapy for approximately 24 hours appears to be safe. However, Heeschen et al. [109] noted that in high-risk patients, if the drug is discontinued for more than 3 days, these patients appear to be at increased risk for a major cardiac complication. It would appear to be prudent to reinstitute the utilization of lipid-lowering agents as soon as feasibly possible.

Beta-Blocker Therapy

The utilization of beta-blocker therapy to reduce perioperative morbidity and mortality in the cardiac patient undergoing noncardiac surgery has gained much favor. The initial study by Mangano et al. [7] noted that with the use of atenolol, the postoperative mortality rate was reduced from 14% to 3% during the first year and 21% to 10% the second year after noncardiac surgery. This study was ultimately substantiated by Poldermans et al. [110] in a retrospective study, which confirmed the benefit of beta-blockade, bisoprolol, in intermediate-risk patients.

However, the study revealed that beta-blockers failed to lower the cardiac event rate in patients who were at very high risk (three or more clinical risk factors and five or more new wall motion abnormalities on echocardiography).

Another study supportive of the use of beta-blocker therapy was that of the previously cited DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group) study [52]. The DECREASE supported the merits of beta-blocker therapy and was a controlled trial study in which 112 patients were randomized to standard care or bisoprolol. The results revealed that 3.4% of the bisoprolol group compared with 34% of the standard group experienced the study's primary end point of either death from cardiac causes or nonfatal myocardial infarction.

Stevens et al. [97], on systemic review, revealed that the utilization of beta-blockers in the noncardiac surgical patient resulted in a reduction of ischemic episodes during surgery (7.6% vs. 20.2%) as compared with placebo. Beta-blockers also appeared to decrease ischemic episodes after surgery and reduced the risk of myocardial infarction and cardiac death. Important to note was that only two trials were performed with high-risk groups.

However, recently, the effectiveness of beta-blocker therapy in the perioperative period has come under question [111,112]. In a large systematic review and meta-analysis of randomized controlled trials, Devereaux et al. [113] came to some interesting conclusions. Perioperative outcomes for the study included total mortality, cardiovascular mortality, nonfatal MI, nonfatal cardiac arrest, nonfatal stroke, congestive heart failure, hypotension needing treatment, bradycardia needing treatment, and bronchospasm within 30 days of surgery.

In 22 trials that were reviewed, approximately 2,437 patients were randomized. The utilization of perioperative beta-blockers did not show any statistically significant beneficial effects on any of the individual outcomes, only nominally statistically significant beneficial relative risk for the composite outcome of cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest. There was also a relative risk in regard to bradycardia requiring treatment and only a nominally significant risk for hypotension needing treatment.

Some of the problems identified in this systematic review were that only a moderate number of events occurred in the perioperative beta-blocker trials. In addition, the meta-analyses revealed a large treatment effect, which is inconsistent with the beta-blocker trials in myocardial infarction and congestive heart failure [114,115]. More importantly, the authors felt that the nominally statistically significant beneficial result of decreased major perioperative cardiovascular events with beta-blocker treatment showed moderate heterogeneity that ultimately weakened the reliability of this finding.

In 2006, the Metoprolol after Vascular Surgery (MaVS) was associated with a reduction in cardiovascular events, but also, treated patients were found to have lower postoperative heart rates and more intraoperative hypotension. Overall, there was not a substantial difference in cardiac events when compared to placebo on 6-month follow-up [116]. The incidence of hypotension and bradycardia was also substantiated in the DIPOM (diabetic postoperative mortality and morbidity) trial [117]. The trial failed to show a reduction in cardiac events in diabetic patients without coronary artery disease undergoing vascular surgery but noted significant hypotension and bradycardia.

Data from the recently concluded POISE (Perioperative Ischemic Evaluation) trial has also added to the controversy [118]. The result of this large, randomized controlled trial in which perioperative metoprolol was utilized, revealed fewer nonfatal myocardial infarction rates and fewer nonfatal cardiac arrests in the treatment group. However, it was also noted that more deaths were in the metoprolol treated group, though they were noncardiac in nature. In addition, more patients in the metoprolol group developed ischemic stroke (41 vs. 19) compared with placebo and for every 1200 patients treated, metoprolol appeared to prevent 15 myocardial infarctions at a cost of eight excess deaths and five disabling strokes.

On a recent analysis of noncardiac surgical randomized trials by Beattie et al. [119], it was recognized that effective control of heart rate is important for achieving improved cardiac outcomes. The cardioprotective effects of heart rate control appear to be evident, but beta-blockers do not appear to reliably

TABLE 149.9

CLINICAL RECOMMENDATIONS FOR IMPLEMENTING BETA-BLOCKERS IN THE PERIOPERATIVE SETTING

Recommendations	Description and rationale
Monitor perioperative heart rate and blood pressure	Serially assess hemodynamic measures at pre-specified intervals. Withhold or administer beta-blocker according to preset thresholds/criteria. Such an approach may help detection of issues such as hypovolemia, infection, sepsis.
Implement a "run-in" phase for perioperative beta-blockade	Initiate therapy at least 7 days before operative intervention. Allows for both acute (hemodynamic) and delayed (anti-inflammatory) effects of beta-blockers. Promotes early recognition of adverse effects (e.g., bradycardia, hypotension, bronchospasm).
Adjust dose to achieve target heart rate of 60 beats per minute, avoiding hypotension	Heart rate control remains the major mechanism of beta-blocker benefit. Helps identify and prevent perioperative bradycardia and intraoperative hypotension. Can require variable doses of drug and thus allows for individualization of therapy.
Recognize that beta-blockers differ considerably	Short vs. long-acting agents, varying clinical effects based on receptor agonism. IV vs. PO route of administration important as IV route can rapidly precipitate side effects. Tailor therapy to maintain same agent/dose (s) as in the preoperative setting.
Continue beta-blockers if already on therapy	Sudden withdrawal of beta-blockers known to cause upregulated beta-receptor state. Class I ACC/AHA recommendation, especially if an original indication already exists. Strive to maintain same agent as the preoperative setting.

Reprinted from Chopra V, Plasiance B, Cavsooglu E, et al: Perioperative beta-blockers for major noncardiac surgery: Primum Non Nocere. *Am J Med* 122(3):228, 2009, with permission from Elsevier.

decrease heart rate in all patients and may be associated with more significant side effects. As such, other medications may be necessary to achieve the goal of heart rate control.

So what to recommend? A recent review by Chopra et al. [120] recognized that though there was a benefit from perioperative beta-blockers, the widespread implementation of perioperative beta-blockade to lower risk groups was probably unwarranted. The group strongly recommended caution when using beta-blockers in patients with low to moderate cardiovascular risk profiles (Table 149.9).

Anesthetic Management and Cardiac Outcome

Currently little is known about the long-term effects of anesthetic management on the cardiac patient presenting for noncardiac surgery. What is known is that there are some well-known predictors of perioperative morbidity and mortality: presence of clinical comorbidities, nature of surgical procedure, and clinical management [121]. Overall, Arbous et al. [122] and Sigurdsson and McAteer [123] have reported that the risk of anesthesia in the immediate perioperative period is remarkably small with a frequency of death attributed to anesthesia to be less than 1 in 200,000 anesthetics. To date there has been no study that has shown a definitive difference regarding the choice of anesthetic technique (e.g., regional vs. general anesthesia) and perioperative outcome.

Monk et al. [124] tried to address the issue of long-term outcomes and anesthesia. The group performed a prospective observational study in which 1,065 patients underwent general anesthesia for major noncardiac surgery. There were no protocols that regulated the type of anesthetic agents used, except for the utilization of Bispectral Index (Aspect Medical Systems, Inc., Norwood, MA) monitoring and electroencephalogram electrode montage. The study revealed that the following preoperative clinical indicators were significant univariate predictors of 1-year mortality: Charlson Comorbidity Score 3 or higher, ASA status III or IV, age 65 or older, history of hypertension, history of coronary artery disease, history of hepatic disease, and history of myocardial infarction. Perioperative factors that were significant predictors of 1-year mortality included: long surgical procedure, intracavitary surgery, longer duration of intraoperative systolic hypotension, and increased cumulative deep hypnotic time (BIS less than 45). Interestingly enough, protective factors that were deemed to be important were advanced education level, larger values of BMI (body mass index), increased preoperative diastolic blood pressure, and high performance on the preoperative Mini-Mental Status Examination.

The results of this study have not been universally accepted, with several criticisms regarding design and data interpretation. Especially difficult to accept were the results surrounding anesthetic depth, cumulative deep hypnotic time, and interpretation of BIS data [125]. Ultimately, studies that are better designed to address these concerns will need to be performed to validate the position of Monk et al.

There is, however, some evidence to support use of inhaled volatile anesthetics over total intravenous anesthesia. Recent studies have suggested a cardioprotective effect of volatile anesthetics. In fact, in the most recent revision of the ACC/AHA guidelines, the authors acknowledge the benefit of volatile anesthetic use in patients at risk for myocardial ischemia [30]. The mechanisms for the cardioprotection are not completely known, but are likely to involve a preconditioning effect, a post-conditioning effect, and an anti-apoptotic effect [126]. These recommendations may help the practitioner decide how to provide anesthesia if general anesthesia is planned; however, they do not aid with the decision between general and regional anesthesia.

SUMMARY

The care of the cardiac patient presenting for noncardiac disease will continue to be challenging. Risk assessment and risk modification continue to evolve, and currently no examination

TABLE 149.10

SUMMARY OF ADVANCES FOR REDUCING PERIOPERATIVE CARDIAC MORBIDITY AND MORTALITY FOR NONCARDIAC PROCEDURES

- Perioperative beta-blockers reduce incidence of cardiac events, however, are associated with complications of perioperative hypotension and bradycardia and possibly stroke [7,110–119].
- Identification of at risk patients continues to evolve [24,29,30].
- Dobutamine stress echocardiography is preferred to noninvasive screening test for identifying patients at risk for postoperative cardiac events [56].
- Routine use of pulmonary artery catheters in high-risk surgical patients is controversial but may be of value [93].
- Myocardial ischemia is reduced with α_2-agonists and statins [94,96,105–108].
- Anesthetic agents may play a cardioprotective role in high risk populations [30,126]

or biochemical marker appears to meet all the criteria necessary. Each of the noninvasive tests previously mentioned have their supporters and detractors, but all have the same goal, that is, to identify the patient at risk who would benefit from further medical optimization prior to undergoing the stress of surgery.

The role for preoperative coronary artery bypass and coronary angioplasty continues to appear to be limited; however, definitive trials are yet to be performed. The utilization of pharmacologic agents such as beta-blockers and statins continue to show great promise but questions also continue to arise, especially when focusing on the risk versus benefits of these therapies. Results of the large, multicenter trials such as the POISE trial have refocused attention to the need of balancing the risk of instituting therapy without regard to the possible detrimental side effects of such medications.

Advances in noncardiac surgery in the cardiac patient, based on randomized, controlled trials or meta-analyses of such trials, are summarized in Table 149.10.

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CHAPTER 150 ■ DIAGNOSIS AND MANAGEMENT OF INTRA-ABDOMINAL SEPSIS

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INTRODUCTION

The intensive care unit is home to a diversity of patients suffering from intra-abdominal sepsis. Patients may be undergoing treatment for a cardiac or pulmonary condition and may develop an intra-abdominal process as an additional insult, or abdominal distention or peritonitis may arise in a patient recently transported from the operating room after an abdominal procedure, and some patients may be new admissions to the hospital with the signs and symptoms of an intra-abdominal infection.

Several principles are crucial to the management of these patients, such as aggressive resuscitation and monitoring, early administration of antibiotics, and careful consideration of an expanded list of differential diagnoses. Also required are thorough assessments of the patient's ability to tolerate various interventions, the importance of gaining source control, and the need for multidisciplinary teams made of intensivists, surgeons, interventional radiologists, and gastroenterologists among others. With the ubiquitous presence of drug resistant organisms, it is imperative to prescribe antimicrobial medications with the mind-set of antibiotic stewardship.

New paradigms are developing in the management of these diseases, such as molecular targets of therapy, delivery of advanced care at the bedside, damage control strategies, and minimally invasive techniques alone or in combination with a definitive surgical procedure.

PATHOPHYSIOLOGY OF THE LOCAL AND SYSTEMIC RESPONSE TO INTRA-ABDOMINAL INFECTIONS

Patients with intra-abdominal infections can be viewed as a unique subset of sepsis syndrome patients. The defense mechanisms of the peritoneal cavity help explain the specific pattern of response seen. Well-defined systems are available for rapid mechanical clearance of foreign particulates and solutes from the intraperitoneal space. Diaphragmatic lymphatic channels provide a means for the entry of peritoneal fluid (and any bacteria or proinflammatory mediators) through the thoracic duct into the venous circulation. Lymphatic capillaries are distributed in the subperitoneal connective tissue of the diaphragm. Mesothelial cells are organized into two discrete populations: cuboidal cells and flattened cells. Gaps (stomas) between neighboring cells are abundant in the peritoneal mesothelium and found only among cuboidal cells [1,2]. The average area of a stoma is approximately 102 μm. Peritonitis increases the diameter of these stomas [3]. Inspiration decreases intrathoracic pressure relative to intra-abdominal pressure, creating a pressure gradient favoring fluid movement across the diaphragm and out of the abdomen. Entry of proinflammatory substances into the lymphatic channels and subsequently the vascular space would be expected to produce many of the hemodynamic and respiratory signs of severe sepsis. Positive-pressure ventilation likely attenuates this process but has not been well studied as a therapeutic maneuver [4].

Other peritoneal defense mechanisms include resident peritoneal macrophages and large recruitable pools of circulating neutrophils and monocytes. These cell types participate in bacterial isolation and abscess formation. Ingestion of microorganisms by these cells may result in secretion of a variety of proinflammatory mediators, including chemokines, cytokines, lipid derivatives, oxidants, and lysosomal enzymes. Manipulation of the number and function of these resident and recruited cells is now possible through the use of colony-stimulating factors, but has not been examined in clinical trials. Similarly, manipulation of the expression of proinflammatory mediators from these inflammatory cells has been postulated to modulate the sepsis response, but clinical trials have been disappointing to date.

The release of proinflammatory products of peritoneal origin into mesenteric, lymphatic, and vascular channels, and this contribution to the systemic septic response has not been fully addressed. Liver dysfunction is common during the course of intra-abdominal infection and occasionally progresses to fatal hepatic failure [5,6]. Considerable evidence supports the notion that various macrophage products, including interleukins-1 and -6 and tumor necrosis factor-α, substantially alter hepatocyte function [7]. In addition to conversion of hepatic synthetic function to acute-phase reactants, serum chemistries reveal evidence of ductal epithelial cytotoxicity, including elevated alkaline phosphatase levels and elevated bilirubin levels. The large number of fixed tissue phagocytes (Kupffer cells) in the liver that are capable of responding to endotoxin absorbed from systemic or mesenteric blood vessels represents a potentially important source of chemokines, cytokines, and other hepatocyte regulatory substances, although portal endotoxemia has not been detected in humans [8,9].

The bacteriology of mixed flora infections, encompassing aerobic, anaerobic, and facultative Gram-negative organisms, explains at least part of the local histopathology of intra-abdominal infection. Facultative and aerobic Gram-negative organisms express and release endotoxin and endotoxin-associated proteins spontaneously, and such shedding is likely intensified by administration of antibiotics [10]. Aside from the potential for inducing the release of cytokines and other inflammatory mediators, these substances induce local thrombosis through a variety of endothelial and macrophage-mediated processes. Synergistic interactions between certain anaerobes, most notably *Bacteroides fragilis*, and endotoxin-bearing Gram-negative organisms suppress local host defense mechanisms and facilitate the establishment of infection [11–13]. *B. fragilis* produces a capsular polysaccharide that interferes with complement activation and inhibits leukocyte function [14]. These phenomena are thought to restrict the delivery of phagocytes to the site of infection, permitting a more rapid rate of bacterial growth than would otherwise be seen.

CLINICAL ASPECTS OF CARE FOR PATIENTS WITH INTRA-ABDOMINAL INFECTIONS

Initial Therapeutic Goals

For the critically ill patient with an intra-abdominal infection, perforation, or ischemic process, timely resuscitation is crucial to their survival. Resuscitative efforts should begin when the patient enters the hospital, rather than waiting for admission to the ICU. During a thorough diagnostic workup with a history and physical, laboratory values and imaging, findings such as severe peritonitis, portal venous gas, or free intraperitoneal air may be discovered that necessitate immediate intervention. In these cases, the need for intervention supersedes the need for ICU admission. Without source control, peritoneal soiling will continue, and the patient's condition will continue to deteriorate. The patient should be prepared for the operating room. Due to the global vasodilatory effects of anesthesia, the patient should receive rapid volume loading. Resuscitative efforts can continue intraoperatively, led by a combined effort of the surgeon and anesthesiologist.

In patients not requiring immediate operative intervention, resuscitation should begin rapidly. Supplemental oxygen should be provided, with a secure airway by endotracheal intubation, if indicated. Lung-protective ventilatory strategy should also be employed to prevent volutrauma, with tidal volumes of approximately 6 ml per kg of ideal body weight [15]. Adequate venous and arterial access should be gained to infuse fluids and blood products as well as provide invasive hemodynamic monitoring and easy blood sampling. Pulmonary artery catheters should be carefully considered, but have proven to be of marginal assistance when the patient is unresponsive to fluid resuscitation [16].

Appropriate resuscitative goals must be established and pursued for each patient, starting by using crystalloid solution to achieve a central venous pressure of 8 to 12 mm Hg. Vasopressors, namely, norepinephrine, should be used to achieve a mean arterial pressure of 65 mm Hg, with supplemental low dose vasopressin use, if necessary. Transfusion of packed red cells should be considered in patients with active bleeding or with hemoglobin less than 7 g per dL, to augment oxygen delivery. In addition to the standard hemodynamic parameters, oxygen delivery parameters such as continuous mixed venous oxygen saturation (SvO2) or mixed central venous oxygen saturation (ScvO2) may be followed. ScvO2 of more than 70% is desirable, with transfusion or pressor therapy to achieve this endpoint. Arterial lactate clearance is another useful parameter. A lactate clearance of at least 10%, measured at 2-hour intervals, has been recently demonstrated to be equal to ScvO2 as an indicator of response to resuscitation. More traditional endpoints should also be considered, such as adequate urine

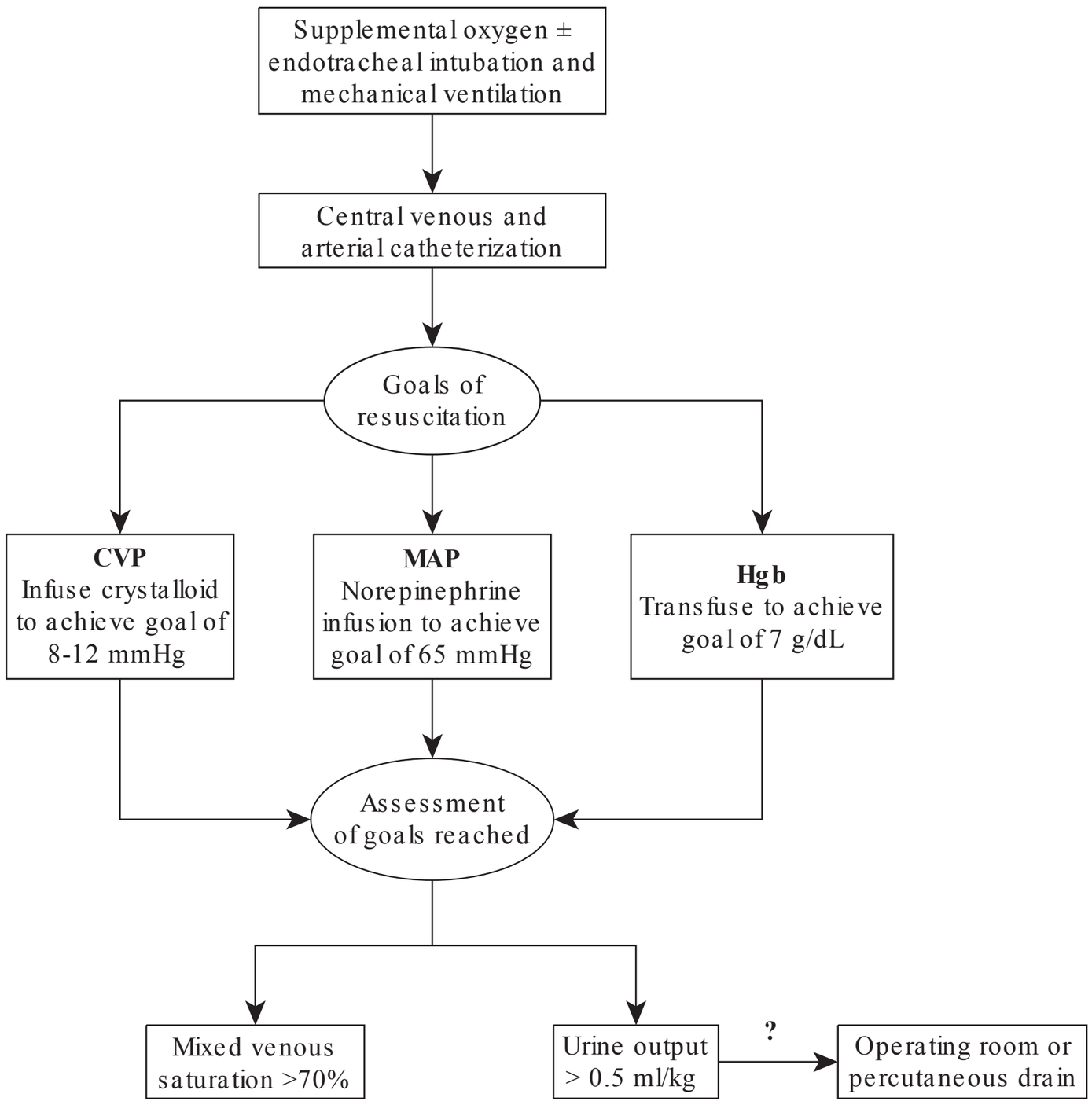

FIGURE 150.1. Algorithm for resuscitation of patients with suspected intra-abdominal infections. Crystalloid or packed red blood cells are infused to achieve goals of resuscitation, while end points are assessed by means of urine output and mixed venous saturation from a superior vena caval sample. Patient responsiveness to resuscitation will dictate whether operative or radiographic intervention is warranted. CVP, central venous pressure; MAP, mean arterial pressure; Hgb, serum hemoglobin level.

output and serial physical exam, specifically extremity warmth and level of consciousness. Newer measures such as tissue oxygen saturation measured by near infrared spectroscopy are being studied and may be beneficial as additional noninvasive means of guiding resuscitative efforts [16–22].

Blood cultures should be obtained upon admission, ideally before administration of intravenous antibiotics. Antibiotic therapy should be started immediately. Broad-spectrum antibiotics against Gram-positive, Gram-negative, and anaerobic bacterial organisms should be chosen. Antifungal coverage should be considered, especially if there is an upper gastrointestinal source, in those on long-term antibiotics or in an immunosuppressed patient [17,23].

Sepsis may be complicated by coagulopathy and DIC. For the patient about to undergo an operation, coagulopathy should be reversed with FFP and/or cryoprecipitate, and platelets should be transfused if counts are less than 50,000 per mm^3. Thromboelastography (TEG) is being increasingly used in ICUs and may prove beneficial for patients with intra-abdominal sepsis [24–26] (see Fig. 150.1).

Surgical Management of Diffuse Peritonitis

First of the surgical concerns during management of any intra-abdominal infection is achieving source control. The infectious or inflammatory process should be removed. All compartments of the abdomen should be explored, including the subphrenic, subhepatic, pelvic, and interloop spaces. All abscesses are drained, all inflamed or perforated bowel is resected, and the abdomen is irrigated with copious amounts of warm saline. The mantra "drainage, debridement, diversion then drugs" expresses the surgeon's opinion about the importance of gaining source control.

After source control is achieved, the surgeon turns their attention to intra-abdominal reconstruction. Primary anastomosis is nearly always performed after resection of small bowel segments. Large intestinal reconstruction is not as straight forward. The majority of data regarding restoring intestinal continuity in the setting of diffuse peritonitis is taken from the treatment of diverticulitis. A two-stage procedure is the default operative mode in sick patients. After resection of all inflamed bowel, this involves creation of an end colostomy proximally and leaving a rectal stump distally, with the intention of restoration of intestinal continuity at a future date. The goal of a two-stage procedure is to avoid anastomotic dehiscence. This procedure is associated with its own morbidities, including stoma complications, abscess formation, and leakage. Primary anastomosis, with on-table colonic washout is increasingly used in perforated diverticulitis, with the goal of avoiding morbidity of stoma complications and need for future laparotomy. Mortality and complications have been shown to be similar to two-stage procedure, with similar operative times. These studies involve heavy selection bias, thus primary anastomosis is still not universally accepted as an alternative to two-stage procedure. The most important factors for the surgeon to consider are the amount of peritoneal soilage and the hemodynamic status of the patient. Patients with perioperative shock, especially those on vasopressors, should not undergo primary anastomosis of small or large bowel [27–30].

In the patient with diffuse peritonitis, after a stoma or anastomosis is created, a drain is usually placed. Closed suction drains (Jackson-Pratt or Blake type) are preferred to open drains (Penrose type). Drain tips are positioned near the inflamed organ, in paracolic gutters or another dependent

portion of the abdomen and exit through the skin and fascia, away from the laparotomy incision. These drains allowed continued efflux of contaminated material from the abdomen. Change in character or quantity of the effluent should raise suspicions of leak or need for further debridement. Absence of drainage, though, may be a sign of a nonfunctioning drain rather than a sign of lack of continued pathology. Drain removal is a variable and stepwise process. Patients often keep drains until enteral diet is tolerated. Occasionally, patients are discharged with drains in place.

A critically ill patient who is likely not to eat in the near future should have a feeding tube placed. Various feeding tubes are used, including nasogastric, gastric, jejunostomy, or g-j tubes, allowing for gastric decompression and jejunal feeding simultaneously.

Though the open abdomen has long been a part of postoperative management of patients, the term "damage control surgery" has only recently been coined. Damage control was first used in the management of traumatic injuries, but is applicable in the setting of inflammatory, infectious, and vascular pathology in the abdomen of a patient in extremis. This process is now the subject of extensive study as a deliberate process in management. The intensivist's role in this strategy is paramount [31].

Damage control surgery (DCS) is defined as an abbreviated laparotomy, consisting of gaining control of bleeding and contamination in a patient on the verge of physiologic collapse. DCS is designed to help solve the problem of the lethal triad of acidosis, coagulopathy, and hypothermia. This triad continues to develop intraoperatively and can lead to patient death despite a technically correct operation [31,32].

Selecting the proper patient for this strategy is based on criteria involving disease process and physiologic status. The decision is made early in the preoperative or intraoperative phase of care by the surgeon, with constant communication with the anesthesiologist. These criteria have been defined by multiple authors. The disease based criteria consist of an inaccessible injury, multiple severe injuries, severe contamination, need for a time consuming procedure, need for a second look to reevaluate the intra-abdominal contents or inability to close abdominal fascia. The physiologic criteria include hypothermia ($< 35^{\circ}$C), metabolic acidosis (< 7.30), nonmechanical bleeding, and poor response to resuscitation [33].

Three general phases of damage control are described. In the initial phase, the abbreviated laparotomy involves a thorough exploration and control of bleeding, and then contamination. No reconstruction efforts are made at this time. The abdomen is closed with towel clamps, a running nylon skin suture, or a layered vacuum assisted closure.

Second is the resuscitative phase. This involves establishing clean IV access and removing femoral lines if possible. A ventilation strategy should have the goal of oxygenation and ventilation while avoiding volutrauma from excess tidal volumes and careful use of Positive End-Expiratory Pressure (PEEP) to avoid diminishing venous return. Fluid and product resuscitation should be used to correct acidosis, restore normal tissue perfusion, and optimize oxygen delivery. This should all be done in a warm ICU room with warm IV fluids to correct hypothermia. Twelve to 48 hours should be allowed for the completion of resuscitation [31–34].

Third is the definitive operation, when packs are removed, the abdomen is reexplored, reconstruction is undertaken, and the abdomen is irrigated [31–34]. Abdominal closure is also part of the definitive operation. Frequently a tension free closure of fascia is not possible. In this case, surgeons often elect for replacing the suction assisted closure in conjunction with a progressive closure strategy. Several strategies exist but all involve changing abdominal dressings every 2 to 3 days and progressively cinching the dressing with re-approximation of the fascia. The goals of these strategies are to provide negative pressure to the wound and continuous evenly distributed fascial traction. Some choose a planned ventral hernia, in which only the skin is closed. This requires reoperation in several months, but avoids placement of a foreign body. Other surgeons perform a fascial closure with absorbable mesh, allow granulation to occur, and then place a skin graft [35–42].

Occasionally, while the patient is undergoing resuscitation, an unplanned operation is necessary. Problems arise such as bleeding, abdominal compartment syndrome, or continued septic shock. Abdominal compartment syndrome is a life threatening condition that develops during resuscitation due to accumulation of fluids and intra-abdominal swelling or due to continued bleeding. Compartment syndrome may present as decreased pulmonary compliance on the ventilator resulting in peak inspiratory pressures more than 40 cm H_2O, as cardiovascular collapse due to decreased venous return or as elevated bladder pressures more than 20 mm Hg with decreasing urine output [31–34].

The intensivist should also be aware of common postoperative problems, namely abscess and fistula formation. If fevers, ileus, or wound drainage arise during this phase, CT scan of the abdomen and pelvis are performed at approximately postoperative day 7. If any suspicious fluid collections are found, they can then be drained percutaneously.

Diagnostic Imaging for Suspected Intra-abdominal Infections

A critically ill patient with a suspected intra-abdominal process and a clinical exam consistent with peritonitis should be taken to the operating room for exploration and treatment. Without such findings on exam, diagnostic imaging is the next important step in the management of these patients.

Routinely, plain abdominal X-rays are obtained. They are easily acquired, have minimal radiation exposure, and can be done at the bedside. The acute abdominal series routinely consists of upright chest, upright abdominal, and supine abdominal films. Plain films have shown the most utility in the diagnosis of the perforated viscous and acute intestinal obstruction. For proper detection of free air, 5 to 10 minutes in the upright position are necessary before performing the study, to allow air to move to a visible location under the diaphragms. If the patient is unable to maintain an upright position, left lateral decubitus position is the next best. Plain films may demonstrate an obstructive process, showing distended bowel loops, step ladder air–fluid levels, and a paucity of distal bowel gas. Frequently however, critically ill patients are unable to sit upright or in a decubitus position for any amount of time. In addition, plain films lack the diagnostic accuracy to discover most intra-abdominal infections, and another mode is needed [43–45].

Computed tomography (CT) is the gold standard for the diagnosis of intra-abdominal processes, their locations and complications, with superior sensitivity and specificity for a range of life threatening diseases including, but not limited to, mesenteric ischemia, hernia, pancreatitis, diverticular abscess, and aneurysmal disease. Helical CT technology has improved both the quality and ease of administration of CT scans. Despite its diagnostic superiority, CT is not without its problems, especially in the ICU setting. Many critically ill patients are unable to be transferred to the radiology suite. Some morbidly obese patients are unable to fit into conventional scanners. CT scans obtained for suspected intra-abdominal infection should be performed with intravenous, oral, and sometimes rectal contrast. Failure to use contrast can significantly decrease

diagnostic accuracy. Many ICU patients are unable to receive contrast, due to renal insufficiency or inability to tolerate orally administered contrast. Decisions about the use of contrast should be made with careful consideration weighing the input from surgeons and radiologists alike [43–45].

Ultrasound (US) is the workhorse of the ICU. In addition to its use as a tool in obtaining central and arterial access, echocardiography, bladder scans, focused abdominal sonogram for trauma (FAST), thoracentesis, and the detection of DVTs, ultrasound is a portable technology with applications in diagnosis and treatment of many intra-abdominal processes at the bedside in the ICU. US is the diagnostic procedure of choice in the setting of right upper quadrant diseases such as acalculous cholecystitis and hepatic lesions, as well as in pelvic diseases including ovarian torsion, PID, and ectopic pregnancy. US is also used at the bedside by the interventional radiologist to percutaneously drain abdominal fluid collections. In addition, US techniques are expanding to include natural orifice translumenal endoscopic surgery (NOTES) procedures for endoscopic ultrasound (EUS) guided drainage of collections in the chest, abdomen, and pelvis. Limitations of ultrasound include poor imaging with increased body wall thickness and bowel gas interference [44–49].

In the era of increasing use of minimally invasive technologies, bedside laparoscopy in the ICU is increasingly common and safe. Bedside laparoscopy can be performed by an abdominal drain tract or new port site. In addition, new devices are being developed that can be used without general anesthesia or pneumoperitoneum. The utility of bedside laparoscopy lies in its ability to diagnose various conditions such as mesenteric ischemia and cholecystitis or for use in trauma, while avoiding the morbidity of an exploratory laparotomy in a critically ill patient [50–53].

MANAGEMENT OF SPECIFIC INTRA-ABDOMINAL INFECTIONS

Management of Abscesses

Once intra-abdominal infection is recognized, and resuscitation and antibiotics have been started, a decision must be made regarding the most appropriate avenue for gaining source control. Percutaneous abscess drainage (PAD) has replaced the need for emergent operative intervention in the management of many intra-abdominal processes [20]. In some patients who become asymptomatic after drainage, PAD provides definitive therapy. In those with ultimately fatal diseases, palliation is provided, and the morbidity of subsequent surgical drainage may be avoided. In other situations, it allows for initial source control and medical stabilization so that an elective one stage operation can be performed. PAD and operative intervention are best viewed as complementary rather than competitive techniques.

Inflammation may manifest as a phlegmon, seen as a viable inflamed mass around the affected tissue, a liquefied abscess, necrotic tissue, or a combination. Liquefied abscesses are drainable, whereas phlegmon and necrotic tissue are not. Decisions regarding which mode of intervention to use are largely based on CT findings and require experience, clinical judgment, and careful consideration of underlying and coexistent disease processes. Close cooperation between the surgeon, interventional radiologist, and other physicians involved in the patient's care is mandatory.

The basic requirements for catheter drainage include a safe route of percutaneous access and a fluid collection of drainable viscosity. Specific indications for PAD have expanded significantly and now include many conditions that were previously thought undrainable, such as multiple or multiloculated abscesses, abscesses with enteric communication, infected hematomas, and deep pelvic abscesses [54,55]. In fact, for abdominal collections that require drainage, PAD is considered the standard, unless a hard indication for an operation exists [54,55]. Advances in endoluminal ultrasound techniques have facilitated advanced drainage procedures. Those abscesses in contact with the rectum or vagina can be treated with catheter drainage through these organs. These ultrasound-guided transrectal and transvaginal drainage procedures are effective and well tolerated [47,56,57].

It is generally possible to distinguish drainable fluid from phlegmon or necrotic tissue using a combination of imaging and fine-needle aspiration. Not all fluid collections require drainage, but intervention is required for those that are infected and for sterile collections that cause symptoms due to mass effect.

It is important to consider the possibility of underlying neoplastic disease in the setting of enteric perforation, especially in elderly patients. Significant soft tissue thickening of the bowel wall, especially if localized and non-circumferential, should raise the possibility of an underlying tumor, as should the demonstration of potential metastatic disease such as adenopathy or liver lesions. A "target" appearance, with circumferential low-attenuation submucosal thickening sandwiched between the enhancing mucosa and submucosa, is believed to be specific for inflammatory disease. To exclude the possibility of neoplasia fully, follow-up imaging is needed to document resolution, or confirmatory tests such as barium contrast studies or endoscopy can be performed.

Technical Aspects of Drainage Procedures for Intra-abdominal Abscesses

Excellent imaging is a key element for successful PAD. Imaging permits precise localization and characterization of disease, appropriate access route planning, and immediate assessment of technical success. Imaging is also needed for adequate follow-up to identify problems and gauge outcome. It is important that the drainage route not cross a sterile fluid collection or other infected space because of the risk of cross-contamination. Crossing the pleural space for thoracic and upper abdominal drainage carries the risk of empyema formation. Thus, collections in the upper abdomen often require an angled subcostal or low intercostal approach [58]. It is acceptable to cross the peritoneal space to drain an extraperitoneal abscess. Placement of a catheter through the small bowel or colon should always be avoided. Transgastric drainage of lesser sac pseudocysts has been advocated by some authors and appears to be safe, although this approach remains controversial [55]. Lesser sac collections also can be approached transhepatically through the left lobe of the liver [59], although traversing solid organs should be avoided whenever possible. Obviously, it is important to be aware of, and avoid, major vascular structures.

In most cases, drainage is performed following fine-needle (18- to 22-gauge) aspiration with the aspirate being used to document infection and gauge the viscosity of the fluid. In some situations, single-step aspiration of the fluid may suffice, without the need for tube placement. Examples include clearly aseptic collections, small abscesses (2 to 3 cm) into which tube placement would be difficult and relatively nonviscous collections that can be completely evacuated. However, for most collections, a drain should be placed to ensure complete evacuation and to minimize the chance of recurrence. If the patient is not already receiving antimicrobial therapy, this should be

instituted before the drainage procedure to minimize the infectious complications of contaminating sterile tissue, although continued antibiotic coverage will be dictated by the contents of the fluid collection.

A multitude of catheters are available for percutaneous insertion. The choice of catheter size is determined primarily by the viscosity of the fluid to be drained. In the majority of cases, 8 to 12 French drains are sufficient [60,61]. Larger drains may be needed for collections that contain debris or more viscous fluid. Drains of larger caliber can be placed at a later time, if needed, by exchange over a guidewire. Although most abscesses can be drained with a single catheter, there should be no hesitation in placing as many drains as are needed to evacuate the abscesses effectively.

After catheter placement, the cavity should be evacuated as completely as possible and irrigated with saline until the fluid is clear. Initial manipulation of the catheter(s) and irrigation should be done as gently as possible to minimize the induction of transient bacteremia and subsequent potential hemodynamic instability. For cavities that are completely evacuated at the initial drainage and for which there are no abnormal communications to viscera, simple gravity drainage generally suffices. For larger or more viscous collections and those with ongoing output due to fistulous connections, suction drainage with sump catheters is more effective [59,61,62]. Thoracic drains should always be placed to water-seal suction to avoid the complication of simple or tension pneumothorax.

Proper catheter management following the initial placement is a critical determinant of success and requires the interventional radiologist to become an active member of the management team [63]. Drains should be checked regularly (at least daily) to monitor the volume and nature of the output, ensure adequate function and clinical response, and quickly recognize and correct any catheter-related problems. Periodic irrigation of the drains is recommended, once or several times per day, with sterile saline [64]. This can be performed by either physicians or trained nurses. Fibrinolytic agents may be useful for evacuation of fibrinous or hemorrhagic collections. Repeat imaging studies and catheter injections are frequently used to document progress and identify problems. Occasionally, it is necessary to add, replace, or reposition drain catheters.

Catheters should be removed when criteria for abscess resolution are met. Clinical criteria of success include resolution of symptoms and indicators of infection. Catheter-related criteria include a decrease in daily drainage to less than 10 mL and a change in the character of the drainage from purulent to serous. Radiographic criteria include abscess resolution and closure of any fistulous communications. If catheters are maintained until these criteria are satisfied, the likelihood of recurrence of the abscess is minimized. For sterile fluid collections, the drain should be removed as soon as possible, generally within 24 to 48 hours, to minimize the risk of superinfection [64].

In evaluating the causes of PAD failure, a number of factors are consistently identified, namely a fluid collection too viscous for drainage and the presence of phlegmon or necrotic debris. Technical modifications such as increasing the drain size and irrigation can salvage some of these drainage procedures. Recognition of phlegmon or necrotic tissue on follow-up imaging studies may lead to cessation of attempts at PAD. Multiloculated collections and multiple abscesses are another cause of failure that can be minimized by using an adequate number of catheters along with mechanical disruption of adhesions with a guidewire. Fistulous communications, either unrecognized or persistent, are yet another potential cause of failure, as is drainage of a necrotic tumor mistaken by imaging to represent an abscess.

Recognition of a significant soft tissue component, maintenance of a high index of suspicion, and the use of percutaneous biopsies can minimize the risk of failing to appreciate the presence of tumor. Suspicious fluid also can be sent for cytologic assessment. The success rate for PAD tends to be lower in immunocompromised patients (53%) patients, as compared to immunocompetent patients (73%) [65].

Appendicitis

Inflammation and infection of the vermiform appendix is the most common intra-abdominal infection requiring surgical intervention [66]. Though the highest incidence is during the first two decades of life, acute appendicitis affects all age groups.

Appendicitis results from obstruction of the appendiceal lumen due to fecalith, lymphadenopathy, foreign body or mass, which initially results in increased luminal pressure, stasis of luminal contents, and soft tissue edema. An intense inflammatory reaction ensues, causing neutrophil infiltration. Venous outflow obstruction develops followed by arterial inflow insufficiency, ultimately resulting in gangrene and perforation.

Classic appendicitis presents with migratory abdominal pain. Initially dull and poorly localized in the periumbilical region, the pain changes to a sharper quality located in the right lower quadrant over McBurney's point. Anorexia is present early and a mild fever is often present. Nausea and vomiting may also be seen, but if they appear early, before development of pain, suspicion should arise for gastroenteritis. Exam reveals focal peritonitis, often evidenced by rebound tenderness, though a cadre of different signs may be elicited [66]. Leukocytosis, if present at all, is mild. Clinical signs of perforation include intense pain, prolonged symptoms, high fever, significant leukocytosis, tachycardia, and severe tenderness [67].

If the diagnosis cannot be made confidently or if perforation is suspected, contrast enhanced CT scan of the abdomen and pelvis may be ordered and has a 95% positive predictive value for acute appendicitis. CT scan may demonstrate appendiceal dilation and wall thickening, periappendiceal fat stranding, appendicolith, phlegmon, abscess, gross perforation, or free fluid [44,68]. Ultrasound is slightly less reliable for diagnosis and demonstration of complications, but is most useful in evaluating for alternate diagnoses, especially gynecologic disorders [68]. Care should be taken to distinguish periappendiceal changes with those around the terminal ileum that may represent inflammatory bowel disease.

Management is started by early administration of intravenous antibiotics covering against Gram-negative bacteria and anaerobes [69]. In acute non-perforated appendicitis, operative intervention should proceed as quickly as possible. Laparoscopic appendectomy is now the procedure of choice, though in thin males open appendectomy is acceptable. Laparoscopic approach provides superb visualization and allows evaluation of other pelvic and abdominal organs [66]. If perforation is found at laparoscopy, the appendix is resected, irrigation is performed, and antibiotics are continued for an extended course of 7 days.

Periappendiceal masses found on imaging may be a phlegmon or an abscess, representing a contained perforation. If feasible, percutaneous drainage of discrete abscesses is standard. If adequate drainage is achieved, management without appendectomy in the acute setting is safe and effective. Less than 10% of patients will fail this approach and require emergent appendectomy [70].

Current controversy exists concerning the need for interval appendectomy (IA) after initial nonsurgical management. Standard for many years was to perform an IA after a resolution phase of 6 to 8 weeks. IA is often a technically difficult operation due to adhesions and distorted anatomy, and many surgeons will elect not to perform IA. This strategy may be most appropriate, as risk of recurrence of appendicitis or

related complication is low, only 5% to 9% in current studies [69–72]. Accurate predictors of recurrence are needed. Also of concern is the risk of malignancy. Appendiceal neoplasm is present in 1.7% of surgical specimens [73,74]. In 1.2% of patients managed nonoperatively, a malignancy was discovered at follow up [70]. Careful consideration of the patient's physiologic status and risk factors must be made.

Diverticulitis

Diverticulitis is an inflammation of colonic diverticula, while these are actually pseudodiverticula – small herniations of colonic mucosa and submucosa through the muscularis [75]. Diverticula develop from a combination of increased intracolonic pressure and mural weakness at the site of blood vessel penetration into the colon [76,77]. The diverticula become occluded with fecal matter. Local ischemia and bacterial overgrowth result in microperforation and the start of the inflammatory cascade [29].

Diverticulitis presents as a constellation of signs and symptoms, most commonly a triad of fever, lower abdominal pain, and leukocytosis. It is typically a disease of older patients, and very rare in patients younger than 40 [78]. Patients also report constipation, recent hematochezia, nausea, vomiting, and dysuria. Pneumaturia and fecaluria are rare, but indicate colovesicular fistula [79]. Diverticulitis is primarily a clinical diagnosis, but contrast enhanced CT is usually performed to assess the location and severity of disease. CT shows colonic wall thickening and fat stranding around an area with diverticula [80]. Masses, fistulas, abscesses, and perforation may also be visualized.

Management is based upon severity of symptoms, number of recurrences, and presence of any complications of diverticulitis. For those with minor symptoms, oral antibiotics can be given, with a gentle resumption of a regular diet. Complicated disease is defined as having a pericolic or pelvic abscess, fistula, stricture, obstruction, hemorrhage, perforation, or diffuse peritonitis [29,81]. For those with complicated diverticulitis, with more severe symptoms or with signs of systemic inflammation, hospital admission, bowel rest, and parenteral antibiotics are mandated after immediate fluid resuscitation [79]. Length of therapy is variable, but usually is continued until leukocytosis is improved, the patient is afebrile, and has decreased abdominal tenderness [29,75,79].

Emergent surgical intervention may be required. Any patient with diffuse peritonitis, obstruction, severe perforation, or not responding to antibiotics alone mandates an immediate surgical exploration and washout with any necessary interventions for repair of colonic perforation [75,81]. Abscesses as a result of complicated diverticulitis are treated similarly as all other intra-abdominal abscesses. In the abscess of generalized peritonitis and hemodynamic instability, well-circumscribed abscesses should be drained percutaneously [75,82,83]. After hospital discharge, patients should undergo colonoscopy, especially in cases of right-sided diverticulitis and those cases with perforation. It is imperative to rule out a potential malignancy. Typically, a 6-week cooling off period is allowed before endoscopy.

Elective surgical intervention is indicated in several circumstances. Those patients with numerous recurrences are at risk for multiple hospital admissions, future complicated disease, and associated colostomy. Elective resection may spare them this morbidity. Complicated disease is much more likely on first presentation, however, and better predictors are needed to determine who will have a recurrence of complicated disease [81]. Any patient having an attack complicated by abscess, stricture, fistula, or contained perforation should undergo elective resection. Patients in whom an underlying colon cancer cannot be successfully ruled out should also undergo interval elective resection [84].

Operative intervention in the elective setting is usually a resection of the affected colon, with colorectal anastomosis. Technique in emergent operations can range from resection of the grossly inflamed tissue and end colostomy (Hartmann's procedure) to resection and primary anastomosis. Both approaches have been shown to be safe, and the decision depends on extent of inflammation and soilage [27,28,30]. The resection of all areas containing diverticula is not necessary, as often they can be scattered about the entirety of the colon [80].

Acute Pancreatitis

Pancreatitis continues to be a difficult disease to treat, despite numerous attempts to clarify and standardize treatment algorithms [85]. The leading causes of acute pancreatitis in North America are biliary disease and alcohol use [86]. The diagnosis of acute pancreatitis is often not difficult – the combination of acute abdominal pain, elevated serum pancreatic enzymes, and nausea and vomiting strongly suggest the diagnosis. The controversy arises in the treatment of complicated acute pancreatitis.

Complicated acute pancreatitis is a disease often encountered in the modern ICU. Patients with pancreatitis often require massive fluid resuscitation and are at increased risk for organ failure [86]. Initial consideration should be given to adequate resuscitation, preserving organ function, providing enteral nutrition, and possibly antibiotics. Although controversy exists for each therapy, the consensus is to resuscitate patients with crystalloid to preserve organ function. Urine output remains the most reliable parameter. Enteral nutrition should be established through gastric feeds to preserve gut immune function and attempt to reverse the catabolic state [86]. Antibiotics directed to Gram-negative and anaerobic flora are reserved for patients with proven infection or prophylactic treatment for those with worsening clinical condition and developing organ failure [87].

Acute pancreatitis is frequently plagued by one of four possible complications – pancreatic pseudocyst, pancreatic abscess, pancreatic necrosis, and infected pancreatic necrosis. Pancreatic pseudocyst is rarely a cause of intra-abdominal sepsis and the natural history of pseudocyst is usually self-limited. If a pseudocyst becomes infected it is classified and treated as an abscess. Percutaneous drainage of infected fluid collections is the treatment of choice and should be undertaken expeditiously once the collections are discovered [88]. Pancreatic necrosis is diagnosed by contrast-enhanced CT scan. Absence of enhancement of the organ strongly suggests necrosis. Necrosis can be missed if CT scan is performed too soon after admission [89]. Treatment strategy is determined by whether the necrosis is sterile or infected. Patients with pancreatic necrosis exhibiting neither organ failure nor hemodynamic instability likely have sterile necrosis. Conversely, patients with worsening clinical conditions despite maximum therapy likely have infected necrosis. Any doubt may be answered by percutaneous image-guided biopsy for culture. The distinction is important since markedly different treatments are employed.

Pancreatic necrosis which remains sterile does not require any additional antimicrobial therapy. Should clinical deterioration occur, it is best to initiate treatment for infected pancreatic necrosis. The treatment for infected pancreatic necrosis is as drastic as it is controversial. Antibiotic therapy should be initiated immediately; a carbapenem such as imipenem/cilastin is recommended [87]. Prophylactic antibiotic coverage for sterile pancreatic necrosis has been proposed to prevent infection, but meta-analysis has not shown this to be true. Sterile pancreatic necrosis should not receive antimicrobial therapy [87].

In addition to antimicrobial therapy for infected pancreatic necrosis, surgical intervention should be considered. The timing and approach of surgical intervention is often debated. Consensus is that if clinically possible, delayed debridement is optimal, resulting in decreased mortality. Pancreatic necrosectomy in the acute stages of necrotizing pancreatitis may become necessary in the clinically worsening patient, but mortality remains exceedingly high [88]. Interest has developed in a minimally invasive approach to pancreatic debridement, using a combination of retroperitoneal nephroscopic debridement, percutaneous drainage, and endoscopic drainage and debridement. These approaches will require further study and have not reached the standard of care in North America [90,91].

Biliary Tract Infections

Acute Acalculous Cholecystitis

Acute cholecystitis in the intensive care setting is a different disease than the stone related disease found in ambulatory patients. Acute acalculous cholecystitis (AAC) is seen in patients suffering from diverse disease processes such as cardiac ischemia, burns, hemorrhage, pneumonia, or severe volume depletion. These patients may be undergoing such treatments as vasopressor support, transfusion, prolonged ventilatory support, high levels of PEEP, prolonged NPO status, and TPN. All of these conditions and treatments are risk factors for development of AAC [92–94]. Acalculous cholecystitis is the gallbladder's reaction to severe systemic illness, rather than a local process as occurs in gallstone related disease.

Decreased digestive stimulation causes stasis, gallbladder distention, and increased intraluminal pressure with associated bile infiltration into the mucosal and muscular layers. There is lymphatic distention and tissue edema [95]. Transfusion of packed red blood cells leads to changes in bile composition and increased sludge [92]. Gut hypoperfusion results in microvascular occlusion and leukocyte recruitment [95–99]. Thus gallbladder empyema, gangrene, and perforation may occur.

Critically ill patients are often obtunded or sedated and are unable to exhibit right upper quadrant tenderness. Hepatic transaminase and alkaline phosphatase levels are often normal and not helpful for diagnosis. A new leukocytosis or fever in a patient with appropriate risk factors should prompt radiographic evaluation, as a delay in diagnosis substantially increases mortality [100,101].

As in all cases of suspected right upper quadrant disease, ultrasound is the initial test of choice. Findings on ultrasound consistent with AAC are pericholecystic fluid, gallbladder distention or elongation, wall thickening, mucosal sloughing, and especially intramural gas [102,103]. Concern exists about the poor accuracy of US in the setting of acalculous disease as there are no standards for the normal gallbladder appearance in critical illness and diagnosis may be missed [104,105]. Since US is quick, portable, and repeatable, accuracy improves upon repeating the exam or using US in conjunction with cholescintigraphy [103,106]. CT scan is most useful in its ability to evaluate the entire abdomen, therefore it is ordered when AAC is not foremost of differential diagnoses. CT is still able to detect AAC in many cases, with findings similar to ultrasound [103,107–109]. Cholescintigraphy, a type of HIDA scan, visualizes injected intravenous radionucleotide buildup in the gallbladder. With intravenous morphine to augment the biliary secretion of the radionucleotide and CCK to visualize gallbladder emptying, superior diagnostic accuracy is achieved [103,105,106]. The large drawbacks of cholescintigraphy is that it is a time consuming test performed in the radiology suite and thus may not be appropriate for critically ill patients.

Antibiotics against Gram-negative rods should begin immediately after the diagnosis is made [69]. Definitive therapy for AAC is cholecystectomy, but treatment strategy is guided by the physiologic status of the patient. ICU patients already suffering complications from their primary, non-gallbladder illness are often unable to tolerate anesthesia and operative intervention. In this setting, percutaneous cholecystostomy under US or CT guidance is safe and effective. With a low failure rate, it can provide adequate source control [110–112]. Open cholecystostomy was performed in the past, but is obsolete in settings where image guided percutaneous drainage is available. When the patient physiologically improves, definitive therapy may be administered by laparoscopic cholecystectomy, on an elective rather than emergent basis [101,103,113]. Only in extremely ill or elderly patients, may cholecystectomy be avoided and cholecystostomy be considered definitive therapy [114].

Ascending Cholangitis

Since Charcot described the elements of "hepatic fever" in 1877, ascending cholangitis (AC) has been consistently defined as having two main features: common bile duct (CBD) obstruction and bactibilia [115]. Today, many of the critically ill patients presenting with AC have recently undergone manipulation of the biliary tract or stent placement. In patients without recent instrumentation, choledocholithiasis, benign or malignant stricture, adenopathy, and postoperative anastomotic stricture are important causes of cholangitis [116–118].

Partial obstruction of the hepatobiliary tract results in higher levels of bactibilia, but any acute obstruction will result in increased intraductal pressures. The increased pressure distends the ducts and increases wall permeability. Translocation of bacteria and toxins occurs and causes systemic toxicity, bacteremia, and hepatic abscesses [118].

The diagnosis of ascending cholangitis is clinical. Charcot described a triad of fever with rigors, right upper quadrant abdominal pain, and jaundice. Reynold's pentad also includes hypotension and altered mental status [119]. These clinical findings are still commonly seen in AC today; however, the classic triad and pentad are only seen in late disease. Patients presenting earlier often have right upper quadrant pain, fever without chills, and hyperbilirubinemia. Elevated transaminases and alkaline phosphatase may also be present due to biliary obstruction and hepatic injury and should not be confused with acute viral hepatitis [115,116].

In the patient with ascending cholangitis, imaging serves several functions—especially confirming diagnosis. Cross-sectional imaging is important for defining the level of obstruction. Etiology and treatment of a proximal CBD obstruction would be quite different than that of a periampullary obstruction. Imaging will also serve to elucidate associated pathology such as hepatic metastasis or abscess. As in all patients with right upper quadrant pain, the initial study of choice is ultrasound [120]. Both ultrasound and CT can accurately detect a dilated CBD and extrahepatic biliary obstruction, but neither can determine the cause and exact level of obstruction, compared to direct cholangiography [121,122]. MRCP is comparable to direct cholangiography in its ability to determine cause and level of obstruction and is noninvasive. Unfortunately, MRCP has a minimal role in the management of acute AC, since these patients will need an invasive procedure for treatment [115,122].

Once a diagnosis of cholangitis is made, prompt initiation of antibiotics and drainage of the biliary tree is required. ICU admission is needed in moderate and severe cases, and aggressive supportive care should ensue. Antibiotic profile should be selected to cover enteric organisms, including *E. coli, Klebsiella, Pseudomonas, and Enterococcus* [115,116]. The preferred method for complete visualization and decompression of

the biliary tree is endoscopic retrograde cholangiopancreatography (ERCP). Bile samples should be sent for culture. If the patient is unstable or all stones are unable to be cleared, a nasobiliary drain should be placed. Nasobiliary drains allow for subsequent imaging and sampling. In a stable patient, after successful removal of all stones, an internally draining stent should be placed [115,123,124]. If malignancy is suspected, brushings and cytology should be performed. If a gallstone is lodged at the ampulla or multiple impacted stones are present, papillotomy is required. Percutaneous transhepatic cholangiography (PTC) may be performed if ERCP provides inadequate decompression, if obstruction is proximal, or if the patient is too unstable to tolerate sedation needed for ERCP. If all interventions should fail, the final and definitive solution may be operative drainage of the bile ducts. After cholangitis resolves, patients will require a definitive operation. Laparoscopic cholecystectomy should be performed for gallstone related disease. Advanced imaging or laboratory studies may be needed for workup and planning for resection of malignant disease [115–118, 125].

Colonic Disease

Clostridium difficile **Pseudomembranous Colitis**

Initially named because of the difficulty in cultivating the bacterium [126], *Clostridium difficile* infection is an increasingly common and severe problem in modern intensive care units. With abundant use of broad-spectrum antibiotics and frequent colonization, *C. diff* associated diarrhea or pseudomembranous colitis is the most common nosocomial infectious diarrhea in adults [127–131].

C. Diff colitis is an opportunistic infection. During antimicrobial therapy for various infections, intestinal flora is destroyed, leaving ample resources for *C. difficile* to multiply. *C. difficile* is a Gram-positive, anaerobic, spore-forming bacillus. This microbe produces two exotoxins, toxin A and toxin B, which are responsible for causing diarrhea, colitis, and systemic illness. Recently, a hypervirulent strain has emerged, BI/NAP1/027, which produces "binary toxin" and increased levels of toxins A and B. This strain has been associated with increased disease severity and recurrence [132–134].

C. difficile infection can manifest in several forms. The most common *C. diff* presentation is colitis with diarrhea, though as many as 20% to 37% [135–137] of patients may have such severe colonic dysmotility that diarrhea is absent. Severe enteritis has been described, and though it is rare, it is capable of producing profound illness [138]. Patients presenting with signs and symptoms of systemic illness are labeled as having severe or fulminant colitis, carrying a mortality rate of 35% [139].

Multiple modalities may be implemented in the diagnosis of fulminant pseudomembranous colitis. In the critically ill patient, the presence of diarrhea is often the first clue. The presence of abdominal distention or peritonitis on physical exam, as well as profound leukocytosis and bandemia are all significant in *C. diff* infection. The gold standard for diagnosis of *C. diff* infection is the notoriously slow cytotoxin assay, which takes 1 to 3 days to result. Most commonly, hospitals use an ELISA to detect the presence of toxin A or B, but these assays have been criticized as having a high false negative rate [135]. Many institutions have established the practice of repeating the test at the next episode of diarrhea to improve diagnostic accuracy. New assays are being tested, which are both rapid and highly accurate [140].

Presence of pseudomembranes, disseminated yellow punctuate mural plaques on endoscopy, can assure the diagnosis. Flexible sigmoidoscopy is commonly performed, but studies have shown poor accuracy in the setting of disease limited to the ascending colon. Colonoscopy of the entire colon may be performed, but would require bowel prep and carries greater risk of colonic perforation in a patient already suffering from severe illness [135,137,141].

In patients with a clinical picture consistent with fulminant colitis, computed tomography (CT) has been found to be the most sensitive measure of colonic inflammation [137]. CT scan may show perforation, colonic thickening, colonic distention, pericolonic inflammation, or free abdominal fluid. CT can localize disease as right or left side predominant or can confirm presence of pancolitis. Though the predictive nature of CT scan is debated, diagnosis made by CT scan, as compared to endoscopy or toxin assay, has been shown to predict survival in patients undergoing colectomy for pseudomembranous colitis [135,141,142].

The mainstay of *C. diff* colitis treatment is medical. When feasible, patients with moderate disease should be discontinued from other antimicrobial therapy. Narcotics, loperamide, Lomotil, or other antimotility agents should also be discontinued, as they promote retention of toxins. Patients should receive general supportive therapy.

Moderate disease is treated with oral metronidazole, with oral vancomycin reserved for recurrent disease. Other antibiotic usage, as well as the duration of therapy is frequently debated. Ten days of therapy after cessation of other antibiotics is considered sufficient [143].

For initial recurrent disease, another round of metronidazole is given, followed by oral vancomycin therapy for a second recurrence. For patients with inability to tolerate oral medications, a nasogastric tube should be used to deliver the medications or vancomycin may be given rectally. Intravenous metronidazole may be added in this scenario, but independently is not as effective as oral therapy [144]. Adjunctive medical therapies may be considered for recurrent disease. Probiotics are frequently used to repopulate gut flora. *Saccharomyces boulardii* is thought to have anti-inflammatory effects on the colon [145]. In small, randomized controlled trials, probiotics have shown a favorable effect. Probiotic cocktails have been shown to both prevent and decrease recurrence of *C. diff* infections [146].

Cutting-edge therapies target the toxin-mediated mechanism of *C. diff* colitis. IVIG administration [147] and treatment with monoclonal antibodies [133] are currently being used in clinical trials. *C. difficile* infections progress to fulminant disease in 3% to 8% of patients [132]. Fulminant or complicated disease is defined variably throughout the literature. Definitions generally include such parameters as need for ICU admission, need for surgery, and presence of shock, respiratory failure, or renal failure.

Physicians and researchers have struggled to find adequate predictors of disease severity. Many recent studies have sought to elucidate exactly which factors predict a patient's risk of mortality. Profound leukocytosis is often seen in *C. diff* infections and several studies show increase in mortality associated with a WBC count more than 20,000 per μL. High band percentage or leukopenia were also associated with poor survival. Patient age more than 70 years, ASA score of 4 or 5, low diastolic blood pressures are all factors frequently associated with poor survival in fulminant disease [50,128,132,139]. Length of stay preceding diagnosis of *C. diff* colitis was associated with decreased survival, both in surgically and medically treated groups [50].

Development of fulminant colitis is a surgical concern, and colectomy can be curative in many patients. The true difficulty for the clinician is discovering a window in which patients with fulminant disease will benefit from colectomy, without exposing excess numbers of patients to the morbidity of surgery. Overall, the mortality associated with colectomy in the setting of fulminant *C. diff* colitis is between 35% and 57%. Several studies call for early surgical management

and even a surgical opinion in all cases of severe disease [128,132,135,136,141,148,149].

Need for preoperative vasopressors was associated with increase in perioperative mortality from 14% to 65% [135]. Similarly, in another study, patients requiring preoperative vasopressors or intubation had an increase in mortality from 16% to 84% [141]. Preoperative presence of acute respiratory failure and acute renal failure have been identified as independent predictors of mortality after colectomy [149]. However, patients having a recent surgical procedure had improved mortality after colectomy (77%), compared to those that did not have a recent procedure (23%) [141].

Though several operative approaches have been described for fulminant pseudomembranous colitis, the operation of choice is total colectomy with end ileostomy. In series where left hemicolectomy was performed, mortality increased from 11% to 14% after total colectomy to 100% after left hemicolectomy [136,150]. The exception to this finding is in right-side only disease, identified on endoscopy. Patients undergoing right hemicolectomy had no decrease in survivals [135]. These data highlight the need for early diagnosis of *C. difficile* infection and early surgical intervention, before the development of organ failure.

Toxic Megacolon

Toxic megacolon (TM) has been recognized as a clinical entity for over 60 years, and is defined as an inflammation of the colon causing progressive dilation in the presence of systemic toxicity [151]. Initially described in patients with complicated ulcerative colitis (UC) or Crohn's disease, it is seen more recently as a complication of many various conditions of the colon. Due to improved management techniques of inflammatory bowel disease (IBD) and increased awareness of associated complications, the incidence of TM has decreased in these conditions. TM is still frequently diagnosed as the initial presentation of previously unknown UC [152–154]. TM caused by *C. diff* colitis is on the rise in modern hospitals due to the increasing severity and incidence of *C. diff* infections. Associated with immunosuppression due to AIDS, CMV colitis is also increasingly common. Salmonella, *E. coli* 0157, Shigella, Campylobacter, amoeba, and other infectious diarrheal illnesses have each been recognized as a cause of TM. TM has also developed after various chemotherapy treatments, bowel ischemia, and treatment with antimotility drugs [155–163]. During a workup for possible TM, it is also important to consider intestinal pseudo-obstruction and actual bowel obstruction, though these patients do not exhibit the systemic illness of TM patients.

On gross pathologic specimens, IBD related TM shows dilation, mural thinning, and deep ulcerations while microscopic examination shows myocyte degeneration, abundant granulation tissue with intact Auerbach and Meissner's plexuses. *C. diff* related disease shows the yellow plaques consistent with that disease. CMV related disease shows inclusion bodies on microscopic specimens [151]. The etiology of toxic megacolon lies in the induction of nitric oxide (NO) in the inflamed colonic tissue. NO has been shown to decrease smooth muscle activity. NO synthase was upregulated in surgical specimens of TM as well as in animal models, which also demonstrated colonic dilation and decreased contractile activity [164,165].

Diagnosis of toxic megacolon first involves key elements in the patient's history. Especially important are a personal or family history of inflammatory bowel disease, symptoms of extraintestinal manifestations of IBD, timing of symptoms of diarrhea, abdominal pain and blood per rectum, recent antibiotic use or hospitalization, HIV status and sexual history, recent travel, recent meals as well as any recent starting or stopping of any medications. Next, determining the level of systemic illness is important. Classic criteria require three of the following: fever > 38°C, HR > 120 per minute, leukocytosis > 10,500 per μL, anemia. In addition, one of the following is needed: dehydration, altered consciousness, electrolyte disturbances, or hypotension. The severity of each of these criteria is not specifically defined [154]. These criteria pre-date modern definitions of SIRS/sepsis, which could be used alternatively. Coupled with these above criteria, radiographic evidence of colonic dilation is required.

Classically plain films have been used to diagnose and follow progression of colonic dilation. Typically, a colon dilated to 6 cm was worrisome of an impending perforation, although large variability is seen. Plain films are also able to demonstrate colonic perforation. Recently, CT scan has been found to be superior to plain films. CT scans of TM patients demonstrate dilation in the right and transverse more than left colon. Diameter of 6 to 10 cm with abnormal haustral patterns is the typical finding. Frequently target or accordion signs are visible. Also, significant ascites and pleural effusions are present. CT does not demonstrate superiority in diagnosing the underlying etiology of the TM, but CT is able to detect complications of the disease that were missed on plain films. These findings include small perforations, abscesses, ascending phlebitis, and septic emboli [151,166]. CT scans should be performed upon diagnosis if possible, but are unnecessary in the severely ill patient.

Management of TM involves aggressive medical treatment from the moment of diagnosis and early surgical consultation. Patients should receive supportive ICU therapies and monitoring. Nasogastric tubes should be placed for decompression. Broad-spectrum antibiotics should be started. Treatment of the specific etiology of the TM should begin promptly. Steroids have been given for patients with diagnosis of toxic megacolon due to Crohn's disease or ulcerative colitis, but extreme caution should be used to ensure that an infectious cause is not present and avoid steroids in such cases. Salicylates should also be avoided in the setting of TM [151,159]. An adjunct to medical therapy is postural therapy. Benefit has been shown to patient rolling or a knee-elbow posture. This is presumed to reduce distention by allowing colonic gas to move distally and be more easily expelled [167,168].

Surgical consultation should be obtained as soon as the diagnosis of toxic megacolon is established. Though medical therapy has been shown to be effective in some cases, many patients will not respond and will need a timely, life saving colectomy. Certain indications for an operation include signs of peritonitis, free air, uncontrollable rectal bleeding, and failure of medical therapy. There is no specific size for colon diameter that necessitates colectomy, rather the overall clinical picture should determine therapy. Controversy exists as to the timing of surgery and the definition of medical failure. Medical failure should be viewed as continued clinical deterioration or progressive colonic dilation. Some patients exhibit marked improvement with medical therapy. Others exhibit prompt deterioration and should be taken to the operating room. Often patients show variable degrees of toxicity and questionable response to therapy (i.e., improvement in heart rate but continue to have fever). These patients may undergo a short trial of medical therapy, lasting 24 to 36 hours, with close examination by critical care and surgical teams. Any sign of complication or worsening condition should be managed operatively [152,153,156,169].

Several procedures are proposed for operative management of toxic megacolon. Overall operative mortality for TM is in the range of 7% to 30%, depending on the timing and type of procedure performed. The procedure of choice in modern surgical care is the subtotal colectomy with end ileostomy, leaving a rectal stump or creating a sigmoid mucous fistula. This procedure removes the diseased colon and leaves adequate tissue for future resection or reconstruction. It can be performed safely and quickly [151–153,156,169].

Postoperative Peritonitis

Postoperative peritonitis (PP) is primarily a consequence of anastomotic leakage (66%), intra-abdominal abscess (13%), or perforated viscous (7%) [170]. Local tissue ischemia, infected hematoma, and bile leakage are also common causes of PP and all have an iatrogenic component [171].

PP is a highly lethal condition, with a mortality rate of 30% [172], in part because it is often diagnosed late, due to ascribing clinical deterioration to other possible primary processes, or the reluctance to admit the possibility of a suture-line dehiscence. Malnourished patients, those with resistant organisms, those with multiple organ failures, and the elderly are all at risk for PP [173].

This diagnosis should be considered in any patient with signs of sepsis who has undergone a recent abdominal procedure, particularly those that included a gastrointestinal anastomosis or diffuse soilage. Laparotomy itself introduces free air into the abdominal cavity, thus pneumoperitoneum is a nonspecific finding in patients during the first few days after operation. Diffuse tenderness may not be uniformly present, as it can be masked by incisional pain. Intra-abdominal fluid is to be expected in the recent postoperative period. However, if US or CT reveals large amounts of fluid or persistent peritoneal fluid, image-guided aspiration should be considered for diagnostic purposes. A Gram's stain that reveals white cells, bacteria, or enteric contents is an indication for immediate laparotomy.

Surgical treatment should include either re-anastomosis in small bowel leaks or end-colostomy in colonic leaks, depending upon the degree of fecal contamination and the patient's condition. Postoperative abscesses should be percutaneously drained with image guidance. Patients suffering from PP who have been hospitalized for several days may be infected with resistant organisms. Cultures should be followed closely and therapy extended if the patient is without clinical improvement [174]. The postoperative patient deserves the highest degree of suspicion for anastomotic leak upon any suggestion that an intra-abdominal process has developed.

Enteric Fistula

Gastrointestinal fistulas are among the most dreaded and difficult to manage complications treated by surgeons and intensivists. A fistula is defined as an abnormal communication between two epithelialized surfaces. Enterocutaneous fistulas (ECFs), connections between bowel and skin, are associated with mortality rates of up to 21% [175] and long, expensive hospital stays. Patients suffering from ECFs are also frequently plagued with such problems as severe fluid and electrolyte imbalances, malnutrition, anemia, sepsis, and difficult wound care issues.

More recently, open-air fistulas, or enteroatmospheric fistulas (EAF) are increasingly common, as a consequence of damage control surgery and the open abdomen. EAFs involve spillage of intestinal contents into an open laparotomy wound, rather than to the skin. This combination of a large open wound and continuing peritonitis leads to a profoundly catabolic state. This is a dire situation, with mortality approaching 65%, considerable patient suffering, and huge demands on resources and clinicians to provide adequate nursing and wound care [175,176].

Enteric fistulas have numerous antecedent causes, including trauma, foreign body, infection, inflammatory bowel disease, radiation treatment, vascular insufficiency, anastomotic leak, inadvertent enterotomy, and other iatrogenic injury. Fistulas are classified as high output (>500 mL per day), moderate output (200 to 500 mL per day), or low output (<200 mL per day). It is also important to classify a fistula according to its site of origin (e.g., gastrocutaneous, colocutaneous). EAFs are classified as superficial or deep, depending on if they drain outward onto the exposed bowel or inward into the peritoneal cavity [175,176].

ECFs typically present as occult sepsis in a postoperative patient, who has a continued postoperative ileus, a distended abdomen, late postoperative fevers, or increasing leukocytosis. Often there are signs of a wound infection followed by the appearance of intestinal contents through the wound. Diagnosis of fistula is a clinical one, made at the bedside, though laboratory and imaging studies are useful in fistula characterization and management. Fistulogram, that is, contrast injected into the fistula or drain under fluoroscopy, is the prime means of characterizing the fistula, providing information about its location and most importantly can show presence or absence of obstruction distal to the fistula, which precludes spontaneous closure in all instances. CT scan is most useful in elucidating intra-abdominal abscess or other pathology and allows for percutaneous drainage [175,177]. Studying the fistula is the clinician's lowest priority among management goals. Stabilization of the patient, protection of the skin, and ramping nutrition up to goal should all be accomplished first.

Management of patients with fistula disease demands aggressive supportive care. Volume replacement and maintenance is paramount, as patients may lose several liters of fluid daily from intestinal contents measured by drains and bags, as well as large amounts of insensate losses from open wounds and increased respiratory rates. Fluid losses should be measured and replaced. Hypokalemia can be a lethal problem commonly seen with high output fistulas, and should be meticulously managed. Patients should be placed on strict NPO status, gastric secretions should be minimized with a proton pump inhibitor and initially a nasogastric tube should be inserted to prevent distal transit of gastric secretions. Octreotide is often used to decrease fistula output by inhibiting pancreatic and intestinal secretions and decreasing intestinal motility [175,176,178].

Wound management is crucial to timely healing of ECFs and requires a thoughtful and imaginative approach by a team including senior surgeons and wound care/stoma specialists. Goals of wound management include protection of surrounding skin, measuring the effluent, and avoiding desiccation of the exposed bowel. Careful efforts should be made to avoid worsening of the fistula or creation of a new fistula in the surrounding area. Skin should be kept clean and dry. Skin protection can be accomplished with duoderm and ostomy glue placed around the wound edges. Effluent can be collected in a standard ostomy pouch or by intubating the fistula opening with a sump or "whistle-tip" catheter on low suction [175,177]. Recent reports show that with painstaking wound care, 37% to 46% of ECFs may close spontaneously [179,180].

Wound management in patients with open-air fistulas is considerably more complex, due to exposed intra-abdominal contents. Approximately 12 to 14 days postoperatively, dense adhesions form between exposed bowel loops, and they become fused. If a deep EAF is present, and the opening is unable to be drained with sumps, free soiling of the peritoneal cavity will continue. Negative pressure wound therapies are now being employed with some success in this situation, as they allow for continuous drainage. Caution should be used to protect exposed bowel from direct suction with plastic sheeting [176,180]. Superficial EAFs can be functionally converted into an ECF by placing a skin graft onto the granulation tissue of the fused, exposed bowel. Once the skin graft heals, an ostomy pouch may be placed over the fistula [175,176]. Patients with EAF may have a difficult, open wound for months.

Prolonged intestinal failure is the hallmark of severe fistula disease and aggressive nutritional support is a chief principle in the management of ECFs. Ongoing inflammatory processes result in increased nutritional need and inefficient use of supplied nutrients. Draining intestinal secretions result in major protein

losses. Patients with high output fistulas have substantially increased nutritional requirements, often more than double their baseline calculated calorie and protein requirements. Additionally, patients will require much higher doses of vitamins and trace elements [175]. Patients with fistula disease may also benefit from immunonutrition supplementation. Glutamine supplementation is thought to normalize intestinal immunology and cytokine profiles as well as reversing intestinal villus atrophy. Other nutrients such as arginine and fish oil are associated with improved outcomes in critically ill patients [181–183].

Patients with low output fistulas should be able to receive the majority of their nutrition enterally, by a low residue, easily absorbable formula. High output fistulas can also be managed with enteral nutrition. Using a feeding tube in the proximal jejunum, sufficient absorption should occur if at least 4 feet of normal intestine exists between the ligament of Treitz and the fistula. If insufficient length is present here, then enteral feeding may be provided with the tip of the feeding tube distal to the fistula. Another alternative for enteral feeding is fistuloclysis, feeding directly into the fistula itself. When enteral nutrition is provided, it is best given in elemental or semi-elemental formulations, which facilitate absorption. Enteral nutrition is believed by many to have equal efficacy in fistula closure to parenteral nutrition, is able to prevent intestinal mucosal atrophy and reduce incidence of other nosocomial infections [175,184–188]. Full enteral nutritional support is not always possible, due to distal obstruction, sepsis, hypotension, or poor absorptive capacity, and additional support is needed.

The widespread use of parenteral nutrition (TPN) has improved fistula management dramatically, allowing patients' nutritional needs to be met when it is not possible to do so enterally. TPN is thought to reduce overall patient mortality and result in increased rates of fistula closure. Parenteral nutrition also allows for custom replacement of micronutrients and trace elements. Unfortunately, TPN carries risks of central venous catheter insertion, increased expense, catheter related sepsis, thrombosis, and TPN associated cholestasis, and liver dysfunction [175,185–188].

Surgical mantra dictates that if ECFs do not heal spontaneously by 6 weeks, then they will ultimately require operative management. Timing of surgical repair is crucial, since early in the postoperative process, patients develop dense adhesions intra-abdominally that prevent access into the abdomen. Most surgeons describe a waiting period of several months before attempting surgical repair. This delay is to allow time for maturation of these adhesions, for resolution of any infectious processes, and for optimization of nutrition.

CONCLUSION

Intensive care unit patients can have primary intra-abdominal infections leading to sepsis or the abdomen may be a source of secondary sepsis in the previously physiologically compromised patient. Regardless of the circumstances, intra-abdominal sepsis requires a stepwise approach that includes prompt and judicious resuscitation, adequate source control, and broad-spectrum antibiotic coverage. Equally important as fluid and medical therapy is an overall design to preserve and restore gastrointestinal function and continuity. A multidisciplinary team approach to essential to succeed in the intensive care unit caring for patients with intra-abdominal infections.

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CHAPTER 151 ■ MESENTERIC ISCHEMIA

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Mesenteric ischemia is a rare, life-threatening condition characterized by compromise of the splanchnic circulation resulting in bowel ischemia. Recognition of this disorder has been increasing, and it is estimated to occur in 1 of every 1,000 hospital admissions [1]. It is often encountered in association with other critical illnesses and has a wide spectrum of clinical presentation, making the diagnosis difficult to establish. In mild cases, asymptomatic reversible mucosal ischemia may ensue, whereas frank bowel necrosis and perforation may follow prolonged malperfusion. The classic finding of pain out of proportion to physical examination is often present, but some patients may have only vague abdominal complaints [2]. Frank bowel necrosis with peritonitis portends a poor prognosis with a mortality rate that can reach 90% [3]. Associated cellular injury often induces a systemic inflammatory response that triggers a cascade of events leading to multiorgan failure and death, even after successful intestinal resection. Effective treatment of this disease requires prompt diagnosis, rapid restoration of circulation, surgical resection of nonviable bowel, and supportive care [4].

ANATOMY OF THE MESENTERIC CIRCULATION

The small bowel and colon are principally supplied by the celiac artery (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). These arteries communicate through an extensive network of collateral blood vessels that can preserve arterial perfusion to the splanchnic organs when one or more of the main arteries occludes or becomes stenotic due to atherosclerotic disease. The gastroduodenal artery and pancreaticoduodenal arcades provide an important source of collateral flow between the CA and SMA. The SMA and IMA communicate through several collateral vessels including the marginal artery of Drummond and the meandering artery also known as the arc of Riolan. The hypogastric artery can provide collateral flow to the IMA through the hemorrhoidal and sacral arteries in the pelvis [5,6] (Fig. 151.1).

ETIOLOGY

Mesenteric ischemia can occur acutely, resulting in rapid development of bowel ischemia, or chronically, producing postprandial pain, fear of eating, and weight loss. Acute ischemia may result from acute arterial occlusion due to thrombosis or embolism, acute occlusion of intestinal venous outflow, or ischemia from impaired flow without fixed obstruction in the setting of sepsis and shock. Chronic ischemia is usually the result of progressive atherosclerotic narrowing of multiple mesenteric arteries.

Acute Mesenteric Insufficiency

Arterial insufficiency accounts for approximately 95% of cases of acute mesenteric insufficiency (AMI) and may be embolic (50%), thrombotic (25%), or nonocclusive (20%). The remaining 5% of cases of AMI are due to mesenteric venous thrombosis [7]. The most common source of arterial emboli is the heart. Patients will typically have a history of atrial fibrillation, myocardial infarction, left ventricular aneurysm, or a prosthetic heart valve [8]. The SMA is the most frequent site of embolization because of the preferential flow pattern established at the origin of the artery where it takes an oblique angle [9]. More than half of the emboli will lodge at or near the branch point of the middle colic artery, a point of anatomic narrowing in the SMA. When this occurs, flow through the proximal jejunal branches continues, producing a distinct pattern of bowel ischemia with preservation of proximal jejunum [10].

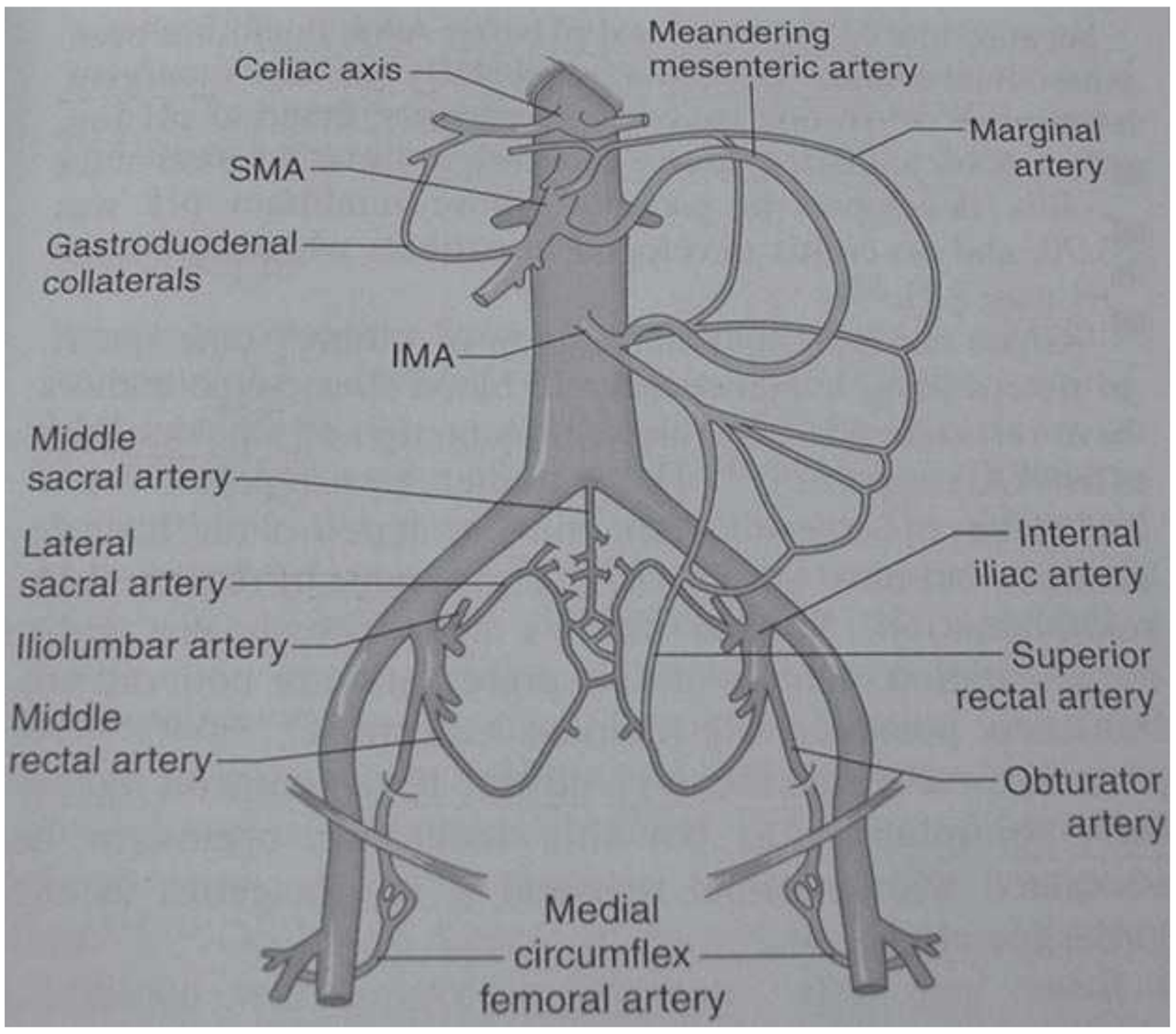

FIGURE 151.1. Schematic of splanchnic circulation. Rutherford Vascular Surgery. Abdominal and Iliac Aneurysms, 1431–1436, Copyright Elsevier (2005).

Acute thrombosis is usually superimposed on chronic coexisting atherosclerotic occlusive disease. The thrombus develops within the proximal SMA or CA in close proximity to the origin of the vessel where it is affected by atherosclerotic disease. In patients with asymptomatic, compensated mesenteric occlusive disease, acute ischemia develops from abrupt thrombosis of a diseased but patent artery (usually the SMA) as a consequence of plaque disruption or flow disturbance beyond a high-grade orificial stenosis [11].

In nonocclusive mesenteric ischemia, the reduction in blood flow usually occurs from low cardiac output or splanchnic vasoconstriction. This is often seen in the intensive care setting, associated with a number of underlying medical conditions such as congestive heart failure, cardiogenic shock, renal disease, hypovolemia, and sepsis [10,12,13]. In addition, vasoactive agents like digitalis and α-adrenergic agonists can induce mesenteric ischemia by splanchnic arteriolar vasoconstriction [13]. Intestinal hypoperfusion can also result from the release of inflammatory mediators associated with severe systemic illness such as pancreatitis, sepsis, trauma, and burns [14,15]. Abdominal compartment syndrome should also be considered as a potential cause of mesenteric ischemia. Excessive intra-abdominal pressure, measured as a bladder pressure more than 25 mm Hg, leads to direct compression of the inferior vena cava and portal vein as well as decreased flow in the inferior vena cava and superior vena cava [16].

Acute mesenteric ischemia may also result from extrinsic mechanical compression of either the arterial or the venous supply to the bowel when local blood supply becomes compromised by a strangulated hernia or intussusception [17]. Sacrifice of a major visceral branch or surgical interruption of the collateral circulatory pathways in the setting of prior visceral artery occlusion may, on rare occasions, result in acute mesenteric ischemia [18]. A well recognized example is ischemia to the sigmoid colon following ligation of the inferior mesenteric artery during aortic resection, or left colectomy, in a patient who has an asymptomatic SMA occlusion and relies on the IMA for visceral perfusion. Aortic dissection may occasionally cause mesenteric ischemia by creating a static or dynamic obstruction at the origin of one or more of the visceral vessels [19]. In this circumstance, perfusion to the mesenteric arteries may be established by either a fenestration procedure or surgical revascularization [19,20].

Mesenteric venous thrombosis (MVT) is an infrequent cause of bowel ischemia. Over 80% of patients diagnosed with MVT are associated with an underlying identifiable coagulation disorder that predisposes them to venous thrombosis. These include both inherited hypercoagulable disorders such as protein C or S deficiency, antithrombin III deficiency, factor V Leiden mutation, and methylenetetrahydrofolate reductase mutations and acquired hypercoagulable states such as malignancy, oral contraceptive use, polycythemia vera, thrombocytosis, trauma, or critical illness [21–23]. The presentation of patients with MVT varies depending on the extent and location of thrombus. Patients typically present with anorexia and nonspecific, vague abdominal pain that may be acute, but is more commonly insidious. Peritonitis is rarely seen and restricted to patients with frank bowel necrosis. The triad of thrombus within the SMV, thickened small bowel wall, and free fluid in the peritoneal cavity as identified on CT maybe an early indication of bowel infarction and the subsequent need for laparotomy [24].

Chronic Mesenteric Insufficiency

Chronic mesenteric ischemia (CMI) results from atherosclerotic disease of the mesenteric arteries and usually requires stenosis or occlusion of two or more mesenteric vessels. Stenosis or occlusion of a single mesenteric vessel will rarely result in abdominal pain; when it does, the SMA is usually the vessel involved. Progression to occlusion most often occurs gradually and allows development of robust collaterals in the splanchnic circulation to compensate for inflow disease. The basal circulation to the intestine is sufficient to maintain adequate blood flow at rest, but when metabolic demands increase, such as in the postprandial state, the higher resistance collateral circulation is inadequate to meet the increased oxygen requirements and symptoms of vascular insufficiency develop. The classic presentation includes a preexistent history of postprandial abdominal pain that results in food avoidance and significant

weight loss. Abdominal pain without weight loss is unusual for mesenteric ischemia and suggests an alternate diagnosis [25].

PATHOPHYSIOLOGY

Mesenteric ischemia occurs when there is inadequate delivery of oxygenated blood to satisfy the metabolic demands of the intestines. The presence of an extensive collateral network in the splanchnic circulation maintains intestinal viability even with as much as a 75% reduction in normal blood flow [25,26]. Under normal conditions, the splanchnic circulation maintains regional blood flow to compensate for systemic changes in hemodynamics through autoregulatory mechanisms. This is achieved by altering the vasomotor tone of the arteriolar resistance vessels. Under circumstances of decreased perfusion pressure, the precapillary arterioles reflexively vasodilate to enhance regional blood flow by lowering mesenteric vascular resistance. A combination of local, humoral, and neural factors mediate the vasomotor tone of these resistance vessels in response to various pathologic conditions [25–27].

In the setting of acute mesenteric thrombosis or embolus, reflexive vasodilation initially occurs and transiently enhances blood flow through existing collateral circulatory pathways. As intestinal ischemia progresses, paradoxical vasoconstriction results and local blood flow is critically reduced to a point where secondary arteriolar thrombosis ensues [28].

Intestinal ischemia from mesenteric venous thrombosis results from venous outflow obstruction leading to venous hypertension resulting in reduction of capillary and arteriolar flow. The thrombosis initially begins in the small veins out in the periphery and extends proximally toward the superior mesenteric vein. Vasospasm of the mesenteric arterioles is also believed to play a major role in ischemia associated with venous thrombosis [28–33].

Early histologic evidence of intestinal ischemia can be observed after only 5 to 10 minutes of arterial occlusion [34–38]. When the ischemic insult is not severe and perfusion can be rapidly restored, these changes are reversible. If ischemic cellular injury persists, tissue infarction will occur, starting from the mucosal surface of the intestine where blood supply is most tenuous. With prolonged ischemia, the bowel wall becomes edematous from increased vascular permeability. Hemorrhage of the mucosal and submucosal layers follows. As infarction extends transmurally, the integrity of the intestinal wall is destroyed and risk of perforation increases. During advanced stages of ischemia, the intestine loses its protective barrier function, resulting in passage of inflammatory cells and translocation of enteric organisms into the portal circulation. Locally produced mediators are released into the circulation along with bacterial endotoxin, triggering an intense systemic inflammatory response. The resulting sepsis and physiologic stress imposed by systemic inflammatory response often leads to multiorgan dysfunction and possibly death [15,39].

CLINICAL PRESENTATION

Mesenteric ischemia can manifest itself in a variety of ways depending on etiology and degree of intestinal ischemia. The signs and symptoms may be subtle, nonspecific, and insidious, especially in chronic and subacute forms of mesenteric ischemia. When ischemia develops acutely, the most common predominant symptom is sudden onset of severe abdominal pain that is often out of proportion to physical findings. However, pain is absent in 25% of individuals with acute nonocclusive ischemia [39]. Symptoms may be nonspecific, including nausea, vomiting, diarrhea, and abdominal distension. Gastrointestinal symptoms may not always dominate the clinical presentation. Acute mental status changes have been reported in 30% of elderly patients with intestinal ischemia [40].

DIAGNOSTIC EVALUATION

Leukocyte count, serum lactic acid level, and arterial blood gas are the most common tests routinely ordered to screen patients for mesenteric ischemia. In patients with acute intestinal ischemia, 75% will have a leukocytosis greater than 15,000 cells per mm^3 and 50% will present with a metabolic acidosis [41]. Unfortunately, abnormalities in these studies accompany other abdominal pathologies, making them nonspecific [42–47].

Plain radiographs lack specificity, and in some cases, abdominal films may even appear normal in the presence of bowel infarction [48]. Some common radiographic features observed in intestinal ischemia include presence of bowel wall thickening, intramural gas (pneumatosis), bowel distention, and mesenteric or portal venous air [49,50]. None of these findings, however, are sensitive or specific to intestinal ischemia. Pneumatosis, when present, is often a sign of advanced ischemia with bowel infarction, although it may also be associated with other acute abdominal conditions such as peptic ulcer and inflammatory bowel disease [51]. The most practical purpose of obtaining plain films in the workup of mesenteric ischemia is often to exclude other causes of acute abdominal pain, most notably gastrointestinal perforations.

Computed tomography (CT) has emerged as one of the most accurate and expeditious methods of diagnosing abdominal pathologies (Fig. 151.2). It is often the first and most common imaging modality employed in the initial evaluation of abdominal pain. Computed tomography is more sensitive than plain films in detecting abnormalities associated with intestinal ischemia such as bowel edema, pneumatosis, and portal venous gas [52]. With intravenous contrast enhancement, CT scanning can assess the mesenteric arterial and venous circulation, permitting detection of both arterial occlusion and venous thrombosis [53,54]. CT angiography (CTA) is the best imaging technique for diagnosis of mesenteric venous occlusion (Fig. 151.3). CTA, however, is not useful in the diagnosis of nonocclusive mesenteric ischemia, and the absence of findings on CT imaging does not exclude the diagnosis of mesenteric ischemia. In recent years, the use of magnetic resonance imaging (MRI) in the detection of intestinal ischemia has been investigated [55–57]. Limited availability, longer scanning time, and higher expense limits the utility of MRI, and it has not been widely accepted in the routine workup of a patient with abdominal pain suspected of having acute mesenteric ischemia [58].

Angiography is used when CTA is inconclusive and when an endovascular intervention is contemplated. Arteriography not only permits endoluminal intervention in select cases of arterial or venous thrombosis, but also allows for selective arterial administration of vasodilating agents like papaverine to counteract vasospasm in patients with nonocclusive mesenteric ischemia [59]. Both lateral and anterior–posterior projections of the mesenteric arteries should be obtained to allow optimal imaging of the proximal and distal SMA and celiac artery [60]. Although effective in identifying arterial pathology, arteriography cannot assess the extent of bowel ischemia or infarction.

Nonocclusive mesenteric ischemia produces a characteristic irregular pruning pattern on arteriography related to segmental vasoconstriction of the arterial branches [60,61] (Fig. 151.4). Acute arterial embolus often demonstrates an abrupt luminal cutoff sign with a meniscus where the clot lodges [62]. In the SMA, the embolus frequently lodges at or just distal to the origin of the middle colic artery and is best visualized on arteriography in the lateral projection. Thrombosis of the mesenteric artery typically occurs at the origin of the vessel where there is underlying arteriosclerotic occlusive disease precipitating the

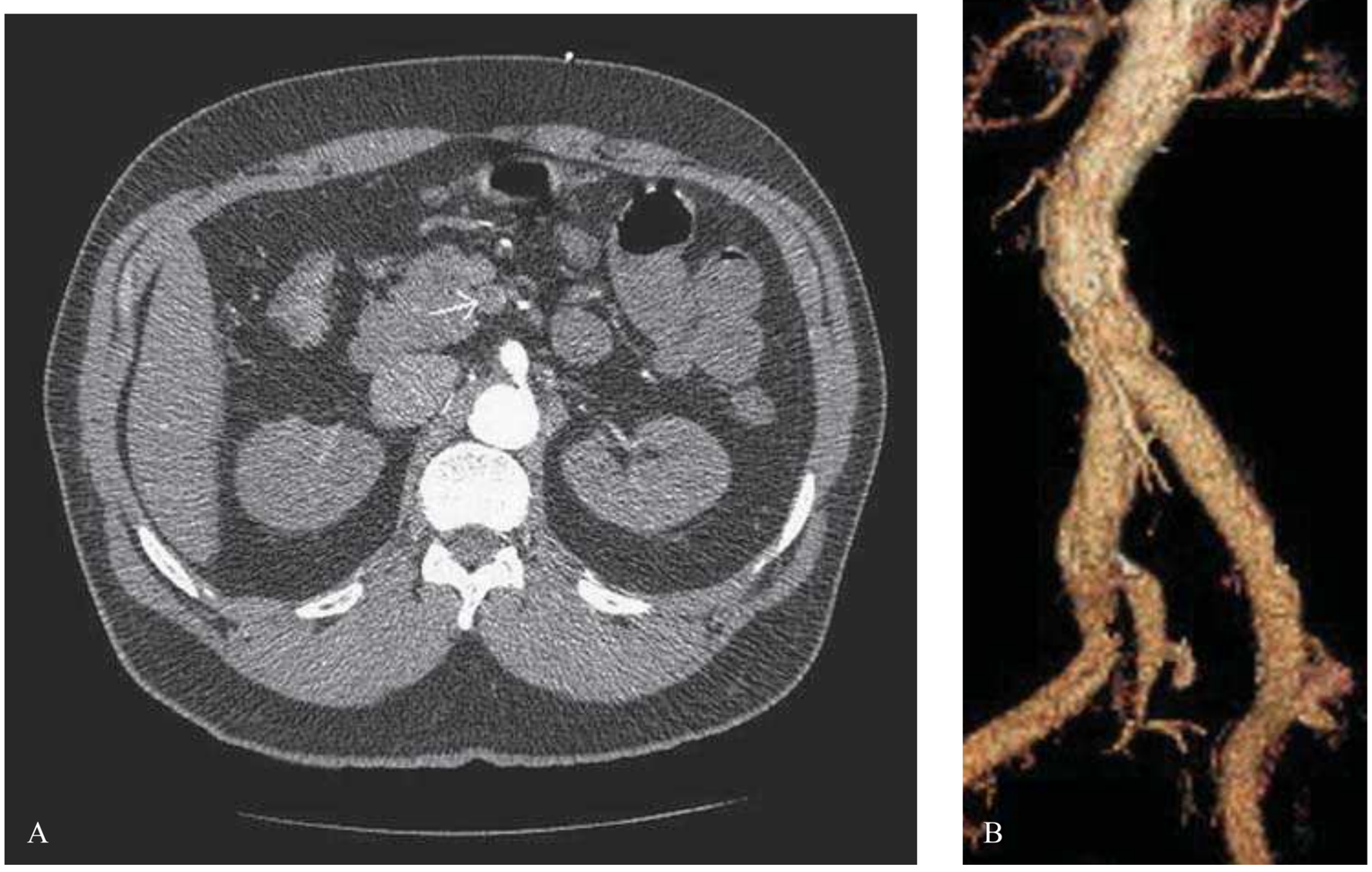

FIGURE 151.2. CTA of patient with mesenteric occlusion axial **(A)**, 3D reconstruction **(B)**.

thrombotic process [60]. There are exceptions to these observations but differentiating embolic from thrombotic disease on arteriography has important clinical implications in planning therapeutic interventions [41,63,64].

Duplex ultrasonography of the mesenteric vessels can be an accurate and cost-effective method of assessing the proximal celiac and superior mesenteric arteries. Ultrasonography can identify the presence of occlusive disease and quantify the degree of stenosis based on velocity criteria [65,66] (Table 151.1). Ultrasound is commonly employed as an initial screening study in the vascular evaluation of symptomatic patients suspected of having chronic mesenteric arterial disease. In addition, ultrasonography can identify nonspecific abnormalities including bowel wall edema, absent peristalsis, and even hepatic portal venous gas [67,68]. Duplex ultrasonography, however, has limited application in the diagnosis of acute mesenteric ischemia due to limitations in its ability to visualize beyond the proximal mesenteric circulation and to insonate through distended bowel.

In the intensive care setting, endoscopy may provide diagnostic alternative in the critically ill patient avoiding the danger of patient transport [69,70]. Endoscopic findings in ischemic colitis can be quite varied. Friable edematous mucosa or patchy areas of mucosal ischemia requires repeat endoscopy and supportive care, while frank intestinal necrosis mandates immediate surgical intervention. Endoscopy is unable to accurately

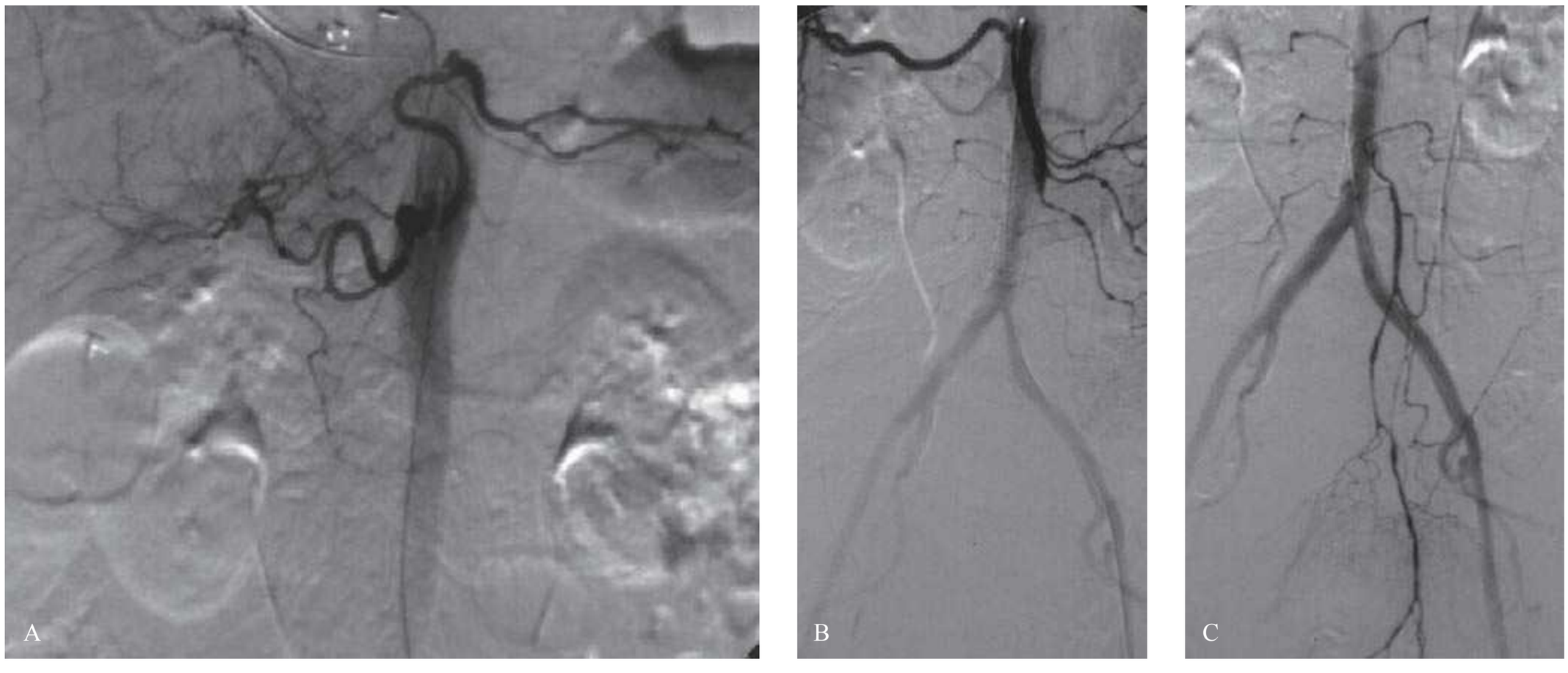

FIGURE 151.3. Beaded appearance of celiac artery **(A)**, superior mesenteric artery **(B)**, and inferior mesenteric artery **(C)** in a patient with nonocclusive mesenteric ischemia.

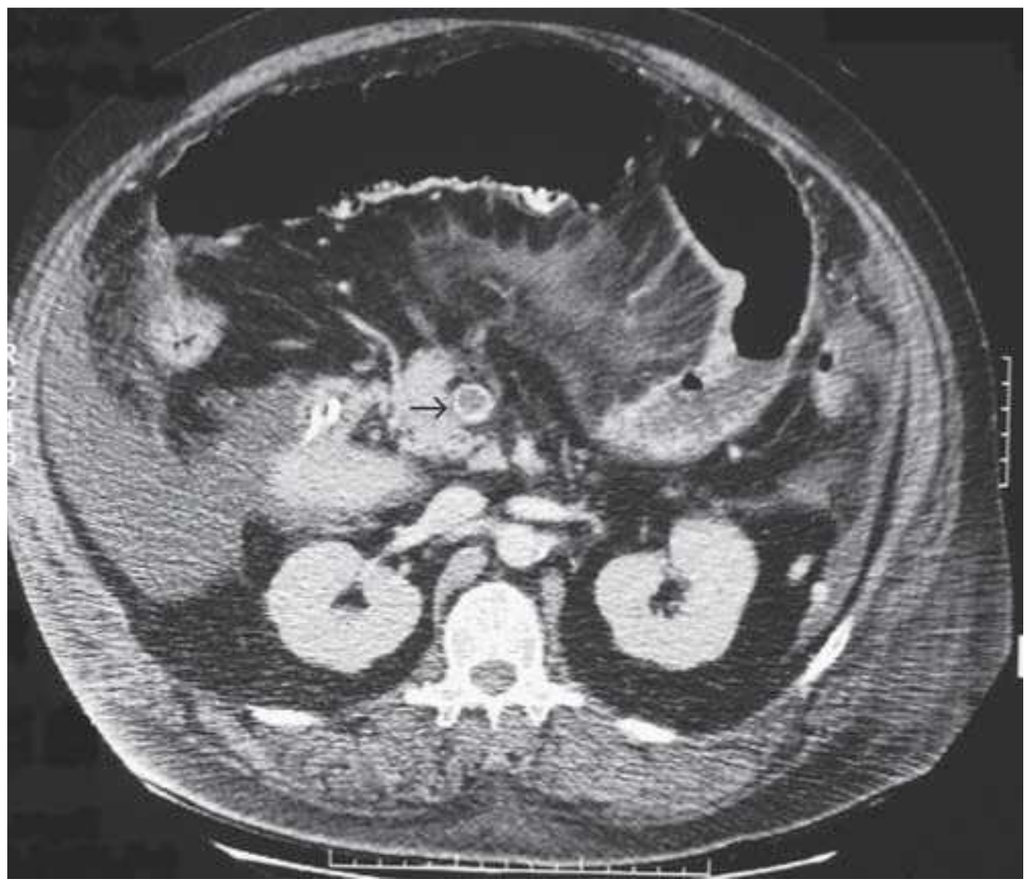

FIGURE 151.4. CT scan showing SMV thrombosis.

assess the depth of ischemic involvement beyond the mucosal surface [71–76], and most of the intestine supplied by the SMA is not readily accessible by conventional endoscopy.

TREATMENT

The treatment of mesenteric ischemia is largely determined by its specific etiology, the duration of ischemic insult, and the extent of infarcted bowel. It is critical to make the diagnosis accurately and expeditiously, initiate treatment to minimize ischemic injury, and preserve intestinal length to avoid the sequelae of short gut syndrome [77,78]. The initial management of patients with mesenteric ischemia involves resuscitation to optimize perfusion and physiologically prepare the patient for possible surgery. Broad-spectrum antibiotics should be initiated for potential infection along with systemic anticoagulation to minimize propagation of the thrombotic process [79]. If symptoms are mild, patients may be considered for immediate arteriography to elucidate the cause of ischemia with consideration of simultaneous catheter-based therapeutic intervention [79,80]. Patients presenting with peritonitis or bowel infarction require immediate laparotomy in lieu of time-consuming diagnostic evaluation that can risk further ischemic injury. The surgical management entails resection of grossly necrotic or nonviable intestine along with embolectomy or arterial revascularization to restore perfusion.

SMA embolus requires surgical extraction of the obstructing clot with assessment of distal perfusion to affected bowel. The arterial vasoconstriction that occurs distal to the embolus can be treated by direct intra-arterial administration of papaverine [81]. Pharmacologic thrombolysis using endovascular techniques has been reported for treating select patients with early mesenteric ischemia without bowel infarction [81–86]. In most cases of acute mesenteric thrombosis, however, severe atherosclerotic occlusive disease is present in the proximal vessel and open revascularization with a bypass is recommended over a percutaneous approach [87,88].

Patients with nonocclusive mesenteric ischemia are initially treated medically to optimize perfusion. The underlying systemic illness is aggressively treated while avoiding any aggravating agents like vasopressors. The diagnosis of nonocclusive ischemia is best made angiographically, which also allows for catheter-based intervention with intra-arterial infusion of papaverine to reverse vasospasm [81]. Patients who have nonocclusive mesenteric disease may still require surgical intervention if the ischemia results in bowel infarction.

Treatment of mesenteric venous thrombosis is focused on systemic anticoagulation with bowel rest. The underlying specific condition or coagulation disorder responsible for causing the thrombotic event should be identified, and the patient should be vigorously resuscitated since considerable third space loss can occur. Surgical thrombectomy of the venous circulation is rarely effective and should be reserved for cases of acute thrombosis without establishment of effective collaterals for venous drainage [89–92]. Patients require systemic anticoagulation in the postoperative period and many may need lifelong therapy due to a hypercoagulable state. Intestinal infarction may be present in the acute form, but the mortality rate and length of involved bowel is less than in acute arterial disease [93]. Preexisting liver disease and previous abdominal surgery, most commonly splenectomy, are two strongly associated risk factors for patients who develop mesenteric venous thrombosis [93].

Patients with chronic mesenteric ischemia have classically been treated with surgical revascularization through either an aortomesenteric bypass or transaortic endarterectomy. More than 90% of the patients will have occlusions in both the SMA and CA [94]. An arteriogram is necessary to determine the location of inflow occlusion and to assess the status of the distal mesenteric circulation for operative planning. Considerable controversy exists regarding the method of revascularization, the number of vessels to revascularize, and the best suited conduit [94]. The two commonly employed methods of revascularization include antegrade supraceliac aortomesenteric bypass and retrograde infrarenal aortomesenteric bypass. In general, antegrade bypass is preferred as the flow is more hemodynamically optimal and the supraceliac aorta is more likely to be disease free. Antegrade bypass, however, involves some degree of renal and visceral ischemia, in addition to increased afterload on the heart. In patients with renal insufficiency or significant underlying cardiac disease, a retrograde bypass, from the aorta or the iliac vessels, may be preferred. However, the rate of symptomatic recurrence is not definitely related to either the method of revascularization or the number of vessels revascularized [12,94]. The goal of multiple visceral revascularization therefore must be balanced against the operative risks entailed in a more extensive procedure.

The endovascular approach for patients with chronic mesenteric ischemia is emerging as a first line treatment option [95–99]. The objective in management of patients with chronic mesenteric ischemia is to relieve symptoms, prevent bowel infarction, and enable weight gain. Total mesenteric arterial occlusions are considered a relative contraindication to endovascular therapy due to fear of distal embolization. Comparisons of open versus endoluminal treatment for mesenteric arterial insufficiency suggest lower periprocedural complications associated with endoluminal techniques, but a higher incidence of late failure [96–99].

In patients with bowel ischemia, determining bowel viability can be the most challenging aspect of the operation. Accurate

TABLE 151.1

DUPLEX CRITERIA FOR MESENTERIC ARTERIAL STENOSIS

Vessel	Peak systolic velocity	Stenosis (%)
Superior mesenteric artery	≥275 cm/sec	70–100
Celiac artery	≥200 cm/sec	70–100

differentiation between viable and nonviable bowel determines the limits of resection and maximizes the residual absorptive reserve of the digestive tract. Determination of bowel viability involves visual and Doppler inspection and if needed a fluorescein-assisted tissue perfusion scan [100]. When bowel viability is indeterminate at initial exploration, a "second-look" procedure to reassess intestinal viability within 24 to 48 hours is used to avoid extensive resection at the first operation [100]. During the initial exploration, grossly nonviable bowel is resected and the intestinal tract is left in discontinuity. The abdomen is closed with drapes or a plastic bag, and the patient is transferred to the critical care unit for aggressive resuscitation and optimization. A second operation is performed in 18 to 24 hours after the patient's condition has been rendered optimal, or earlier in cases of deterioration.

The high mortality rate traditionally associated with intestinal ischemia has decreased in recent years with advancements in surgical revascularization and postoperative critical care. Contemporary studies on survival rates in patients with acute mesenteric ischemia have identified several factors associated with higher mortality: advanced age, inadequate intestinal resection, and presence of nonocclusive mesenteric disease [12]. An aggressive approach to diagnosis and treatment, employing liberal use of arteriography and minimally invasive techniques combined with traditional surgical intervention increases survival [95]. Open surgical revascularization is associated with lower rates of symptom recurrence compared to percutaneous treatment [96]. The most common cause of postoperative death is multiorgan failure followed by cardiovascular complications. Even with successful treatment, long-term survival for patients with acute mesenteric ischemia is generally poor with the majority of deaths related to coronary artery disease, short bowel syndrome, or recurrent mesenteric ischemia [12].

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CHAPTER 152 ■ COMPARTMENT SYNDROME OF THE ABDOMINAL CAVITY

AJAI K. MALHOTRA AND RAO R. IVATURY

ABDOMINAL COMPARTMENT SYNDROME

Introduction

The association of elevated intra-abdominal pressure (IAP) and organ system dysfunction was described as early as the mid-nineteenth century [1]. However, the acceptance of this association as a distinct nosologic entity—abdominal compartment syndrome (ACS)—happened only in the late twentieth century. Even now, more than 20 years after the phrase was coined by Kron et al. [2], there is disagreement as to whether ACS is a distinct clinicopathologic entity in which the organ system dysfunction is causally related to the elevation in IAP or whether the elevated IAP is merely an epi-phenomenon observed in some critically ill patients, especially those receiving large volume crystalloid resuscitation [3]. The reasons for this are many and include (1) the variability of normal IAP [4], (2) lack of agreement as to the best method of measuring IAP [5], (3) lack of agreement about the level of IAP that is well tolerated and any elevation beyond which leads to pathologic consequences in the form of organ system dysfunction (Fig. 152.1) [6], (4) lack of agreement as to when intervention is necessary—in the prodromal phase to prevent development of organ system dysfunction or only after there is evidence of organ system dysfunction [7], and (5) the ideal intervention. These reasons not withstanding, the sheer volume of literature published about all aspects of this condition over the last two decades has reduced the army of skeptics to a corporal's guard. The current chapter focuses on the current understanding of ACS and attempts to provide a practical approach to the diagnosis, and management of this potentially devastating condition.

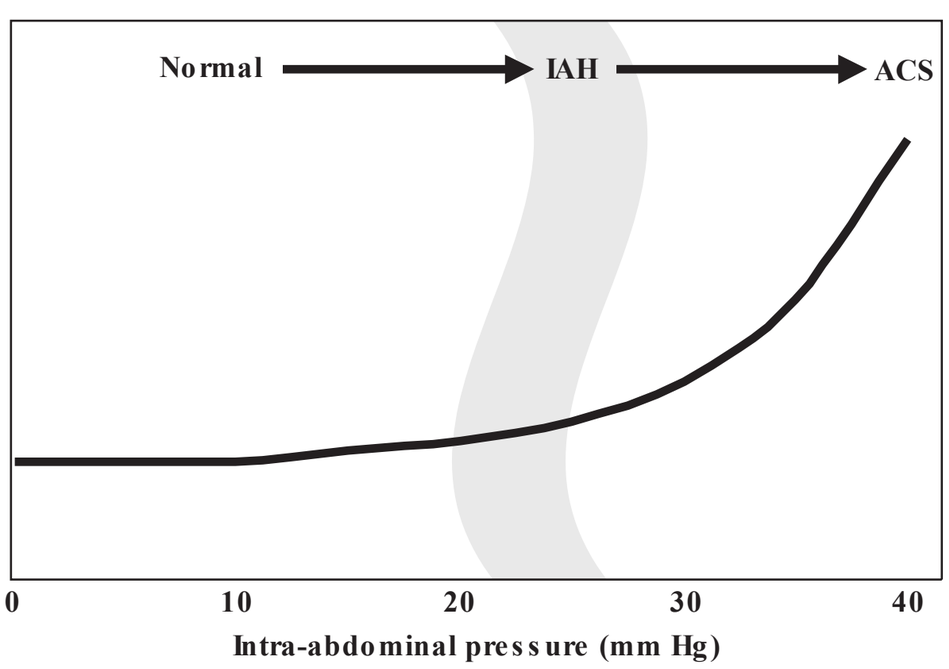

FIGURE 152.1. The continuum of normal intra-abdominal pressure to intra-abdominal hypertension (IAH). As the level of IAH increases organ dysfunction appears and the condition is called abdominal compartment syndrome. Note that the boundaries of normal IAP/IAH and IAH/ACS are wavy (grey zone). These boundaries are different in different individuals and also under different physiological state in the same individual.

The abdominal cavity is a space defined partly by rigid and inflexible structures—pelvis, spine, and coastal arches—and partly by more flexible structures—the musculoaponeurotic abdominal wall and the diaphragm. The total volume that can be accommodated within the confines of the abdomen is limited by these anatomical boundaries. Whenever there is a discrepancy between the available space, defined by the anatomical limits of the abdominal cavity, and the sum total volume of intra-abdominal structures—fluids and intra-abdominal organs—the pressure within the abdominal cavity tends to rise. This situation may arise from any condition that leads to increase in the total volume of structures—accumulation of fluid or swelling of organs—or decreased space—vigorous muscle contraction, loss of domain, etc. Initially the discrepancy is well tolerated by stretching of the flexible boundaries. However, as the limits of this accommodation are reached, even small increments in the intra-abdominal volume lead to large increases in IAP [6]. The elevated IAP affects organ system function in multiple ways. In the initial stages there is a purely mechanical effect best observed in the respiratory system, with embarrassment of ventilation due to elevation of the diaphragm, and in the kidneys where there is a fall in the glomerular filtration pressure affecting renal function. As the IAP continues to rise, there is decreased venous return to the heart affecting cardiac function and resulting in decreased cardiac output (CO). This reduction in CO has profound effects on every cell within the body as it globally decreases tissue perfusion. Finally, there is evidence that the elevated IAP in and of itself acts as a potent pro-inflammatory stimulus augmenting the systemic inflammation already set in motion by (1) the primary process that initiated the elevation of IAP and (2) tissue hypoperfusion caused by the diminished CO.

Definitions

As already mentioned earlier, there are no uniformly accepted definitions of the terms used in the context of ACS. Often, ACS and elevated IAP are used interchangeably, and the units of pressure measurement vary between mm Hg and cm H_2O. At the first World Congress on Abdominal Compartment Syndrome held at Noosa, Australia, in December 2004, attempts were made to develop consensus definitions of these terms and also to standardize the units and methodology used for measuring IAP. The definitions that follow are those that were developed at that conference and are used throughout the chapter. The units used are mm Hg unless otherwise specified. The method used to measure IAP, unless otherwise specified, is by the well-described technique of measuring bladder pressure, where the level of the pubic symphysis is considered 0 mm Hg [8].

Normal IAP: IAP varies between subatmospheric to a mean of 6.5 mm Hg [4]. It is affected by body habitus (chronically elevated in morbid obesity) [4], phase of respiration (higher during inspiration), and body position (elevated in the erect position) [5].

Consensus definition: IAP to be considered normal should be measured in the supine position, at end expiration and should have a value < 10 mm Hg [7].

Elevated IAP—intra-abdominal hypertension (IAH): Brief elevations of IAP are fairly common and seen during sneezing, coughing etc and are of little clinical significance. Even in critically ill patients, brief elevations maybe observed during changes in body positions etc and are likewise clinically unimportant [4]. For IAP to be considered elevated, in a clinically significant fashion the elevation has to be sustained. The value at which IAP is considered elevated is a matter of debate; however, since alterations in physiology maybe observed even at relatively mild elevations to about 12 mm Hg, this value is the one supported by consensus.

Consensus definition: IAH should be defined as peak measured IAP of ≥ 12 mm Hg on two measurements 1 to 6 hours apart [7].

ACS: The point at which IAH develops into ACS remains controversial. Although it is generally agreed that ACS is the association of IAH, causing one or more organ system dysfunction, how the organ system dysfunction should be identified is not as well defined. When very sensitive and often invasive measures of organ system dysfunction are used, even minor elevations of IAP have been shown to affect function (Fig. 152.2) [9]. Also organ system function maybe affected at a certain IAP in one individual whereas the same level of IAP may not significantly alter organ system function in another individual [4]. Second, the level of IAH that is well tolerated can be different under differing physiologic states even in the same individual. For example, the threshold at which IAH leads to organ system dysfunction is significantly lowered posthemorrhagic shock as compared with baseline conditions [10]. Last, there is evidence that primary ACS (caused by an intra-abdominal pathology—see later) is less well tolerated than secondary ACS [11] (caused by resuscitation in the absence of significant intra-abdominal pathology—see below).

Consensus definition: ACS should be diagnosed in the presence of (1) peak IAP of ≥ 20 mm Hg on two measurements 1 to 6 hours apart and (2) one or more organ system failure that was not previously present as defined by sequential organ failure assessment (SOFA) score of ≥ 3 (or an equivalent scoring system) [7].

Types of ACS: Initially ACS was described after intra-abdominal catastrophe—traumatic or inflammatory—and termed primary ACS [2]. More recently, it has been recognized that ACS can also develop in the absence of abdominal injury/pathology. This is usually observed in patients requiring massive volume resuscitation for any form of shock, usually traumatic or septic. It is believed that this form of ACS, termed secondary ACS, is due to leakage of fluid from within the capillaries resulting in massive edema of the intra-abdominal organs causing increased volume [11,12]. At times, the two conditions may coexist as in a patient with an intra-abdominal injury/pathology who during the recovery phase develops pneumonia and sepsis resulting in leaky capillaries. Recurrent ACS may be observed following therapy for either primary or secondary ACS, and this has been called tertiary ACS [13]. Finally, a very early hyperacute form of secondary ACS has been recognized that develops while repair of extra-abdominal injuries is being carried out simultaneous with massive volume resuscitation required for the hemorrhagic shock produced by the extra-abdominal injury [11]. Previously, hyperacute ACS was used to describe physiologic, transient, clinically insignificant elevations of IAP observed during sneezing, coughing, etc [14].

Consensus definitions

Primary ACS: Primary ACS is defined as ACS developing in a person where the proximate cause of the ACS is intra-abdominal/pelvic pathology that usually requires abdominal surgery and/or angio-radiologic intervention. The pathology may be traumatic, and/or inflammatory in nature [7].

Secondary ACS: Secondary ACS is defined as ACS developing due to increased volume of intra-abdominal contents from accumulation of fluid and/or visceral swelling, and where the proximate cause of the increase in volume is not any intra-abdominal/pelvic pathology requiring abdominal surgery and/or angio-radiologic therapy. Secondary ACS is usually observed during massive volume resuscitation for major nonabdomino/pelvic injuries, burns, severe acute pancreatitis, septic shock from a nonabdomino/pelvic infective source, etc [7].

Tertiary ACS: Tertiary ACS solely refers to ACS that develops or persists despite previous attempts to prevent or treat primary or secondary ACS [7].

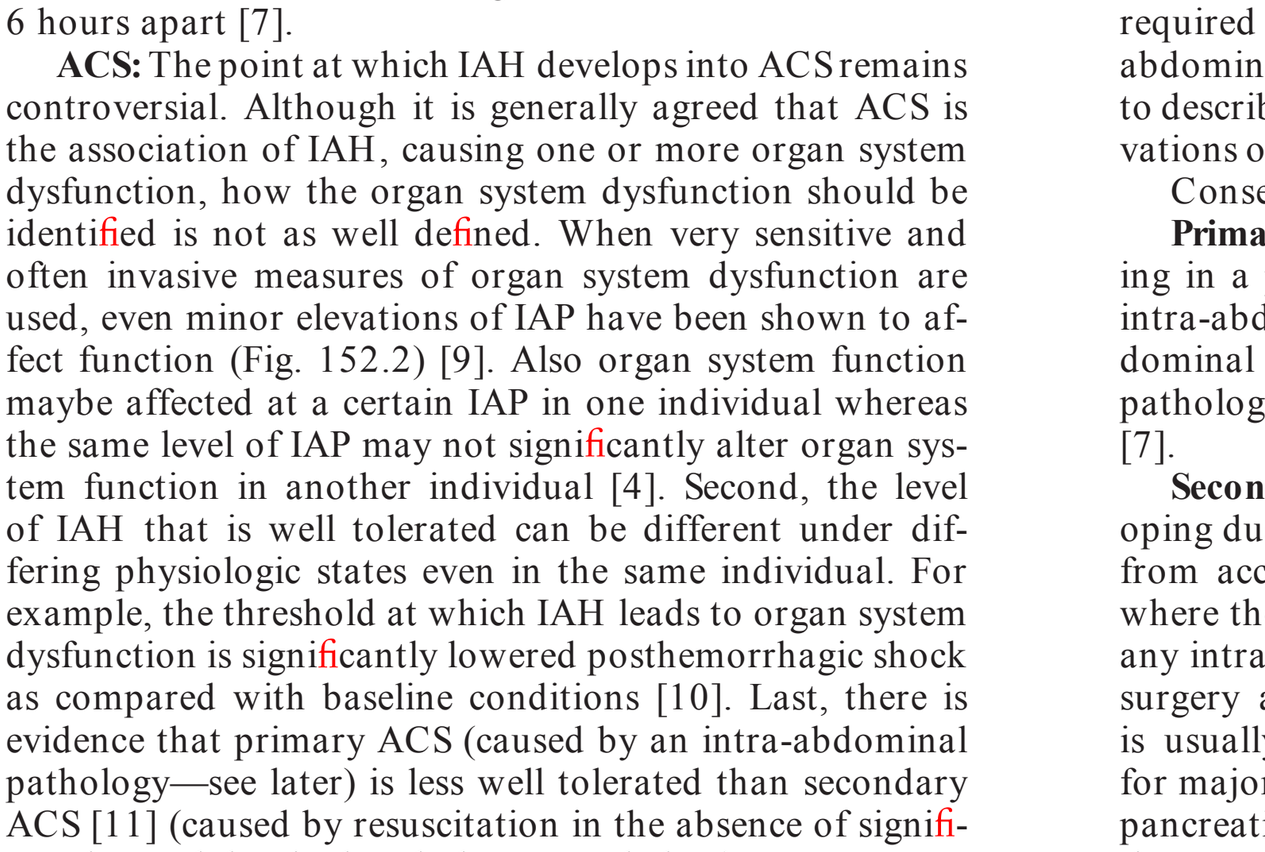

FIGURE 152.2. Effect of increasing intra-abdominal pressure on cardiac output (CO), hepatic artery flow (HA), superior mesenteric artery flow (SMA), and gastrointestinal mucosal flow (mucosa). Note that the splanchnic and mucosal flows start to decrease even at fairly low levels of intra-abdominal hypertension and even when global CO has not been affected.

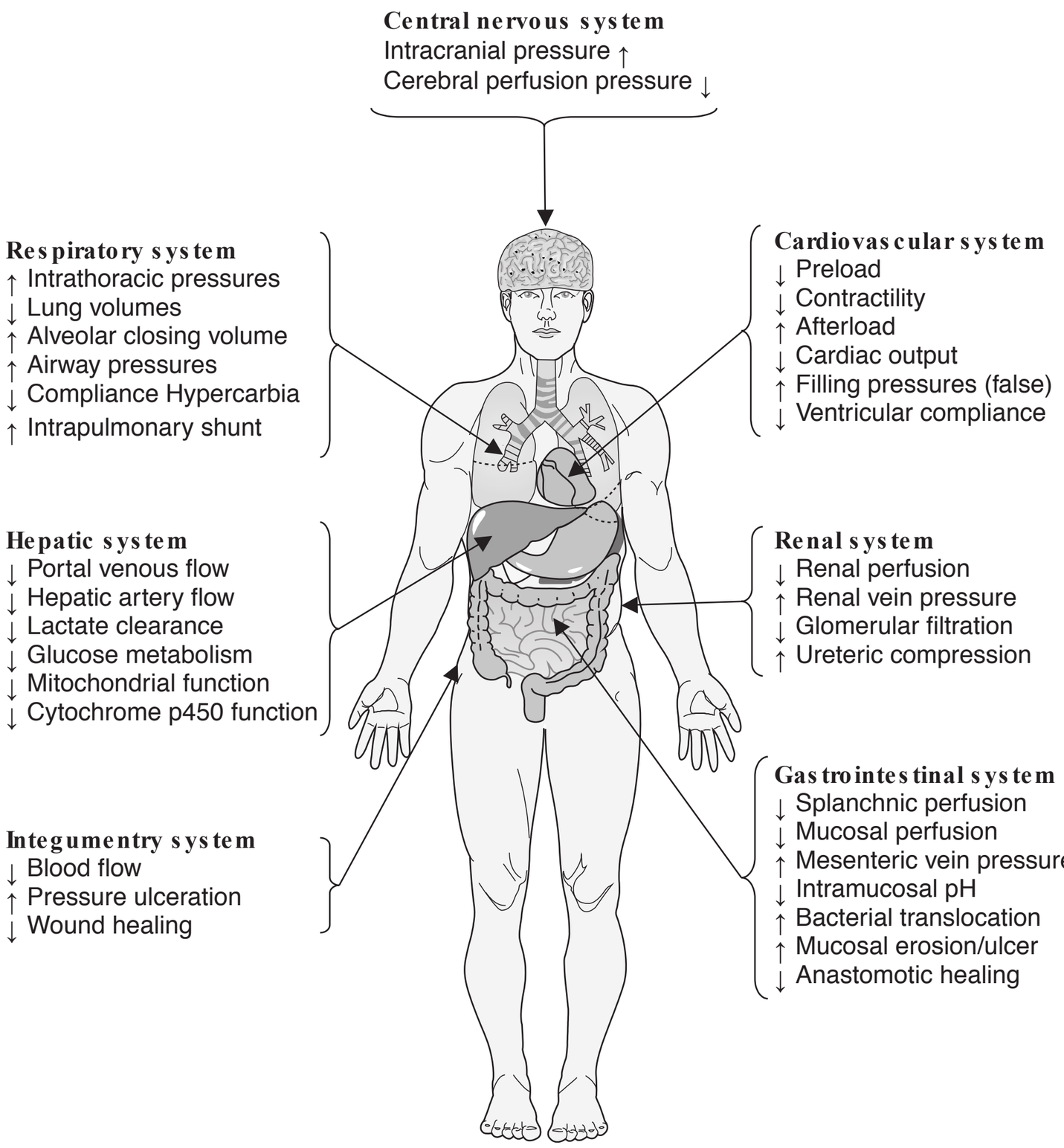

FIGURE 152.3. Effect of abdominal compartment syndrome on various body systems.

Hyperacute ACS: The term should be reserved for a very early form of secondary ACS that develops while surgical and/or angio-radiologic control of an injury is being carried out simultaneous with massive volume resuscitation for the shock caused by the same injury [11].

Impact of ACS on the Body

ACS has profound and far reaching effects on every major organ system of the body (Fig. 152.3). As mentioned earlier, these effects are related to (i) the mechanical pressure caused by IAH, (ii) the reduced perfusion to the tissues caused by diminished CO, and (iii) ACS amplifying the systemic inflammatory response already in motion due to the primary pathology, its treatment and tissue hypoperfusion.

Cardiovascular Effects

ACS affects each of the three determinants of cardiac function—preload, contractility, and afterload. IAH leads to compression of the inferior vena cava decreasing venous return from the lower half of the body [15]. In addition, elevated IAP raises the diaphragm leading to increased intrathoracic pressure, further impeding venous return to the heart [16]. Paradoxically, the central venous and the pulmonary capillary wedge pressures actually rise leading to a dissociation between the commonly used measures of cardiac filling and true cardiac end diastolic volumes. This increase in the filling pressure is merely the transmission of increased intrathoracic pressure to the measured intravascular pressure and not a true reflection of intravascular volume and cardiac filling [17]. Other techniques that directly measure cardiac end diastolic volumes tend to give a more accurate picture of cardiac filling [18]. The decreased venous return and cardiac filling negatively impact cardiac contractility. In addition, ACS directly leads to a decrease in ventricular compliance further affecting cardiac filling and contractility [15]. The effects of elevated intrathoracic pressures are more prominent on the right ventricle. Normally the right ventricle acts more as a conduit than as a pump. The elevated intrathoracic pressures however lead to an increase in pulmonary vascular resistance due to direct compression of the lung parenchyma leading to an increase in right-sided afterload. To overcome this increased right-sided afterload, the right ventricle has to play a more active role if left ventricular filling is to be maintained [19]. Last, ACS leads to an increase in systemic vascular resistance—left-sided afterload—that initially may cause the mean arterial pressure to rise; however, as the CO continues to fall, the net result is a lowering of systemic blood pressure, further compromising perfusion [20]. The diminution in CO can be partially ameliorated by volume loading [15,16,20]. However, for a sustained improvement in systemic perfusion, the ACS needs to be treated usually by abdominal decompression.

Respiratory Effects

The direct mechanical effect of elevated IAP results in the diaphragm moving cephalad into the chest [21]. This results in a reduction in minute ventilation leading to hypercarbia and

respiratory acidosis. The compressive effect also leads to an increase in pulmonary closing volume and decrease in functional residual capacity and lung compliance [16]. The effect of these later changes is a mismatch between ventilation and perfusion and increased right to left shunting causing hypoxia. Clinically the earliest observed change is an increase in peak airway pressure, or if the patient is on a pressure limited ventilatory mode, a decrease in tidal volume [16]. If the ACS is not treated at this stage, the full effects on the respiratory system are observed with hypoxia, hypercarbia, and respiratory acidosis [16]. The hypoxia caused by the respiratory system effects adds to the tissue hypoxia produced by the diminished tissue perfusion due to the cardiovascular effects of ACS.

Renal Effects

ACS causes direct compression of the renal parenchyma causing elevation of renal venous pressure and increased renal vascular resistance [22–24]. In addition, the reduction in CO leads to diminished perfusion to the kidneys [20]. The end result is a reduction in urine production and, if left untreated, overt renal failure. Decreased urine output is often the first sign of developing ACS. Increasing CO only partially compensates for the reduction in glomerular filtration pressure, and insertion of ureteric stents offers no benefit [25].

Splanchnic and Hepatic Effects

While difficult to observe clinically, animal studies have demonstrated profound reductions in mesenteric and hepatic blood flow occurring with ACS. The reduction in flow is disproportionate, that is, it is observed whenever IAH is present even in the absence of significant hypotension and decrease in CO (Fig. 152.2) [26]. Within the bowel, the mucosa seems to be the most sensitive to these reductions. Initially, the reduced flow leads to increasing mucosal hypoxia and acidosis [27]. In later stages frank mucosal ulceration maybe observed. The net effect of these changes is loss of the selective absorptive function of the mucosa causing increased bacterial translocation and production of oxygen free radicals [28]. The exact consequences of bacterial translocation into the mesenteric venous and lymphatic systems are not clear. Some continue to believe that bacterial translocation may be responsible for driving the systemic inflammatory response [29]. Besides increased translocation, there is evidence that ACS, by decreasing mesenteric perfusion, may negatively impact healing of intestinal anastomosis [30].

Central Nervous System Effects

Elevated IAP leads to elevations in central venous pressures that are directly transmitted to the venous outflow from the cranial cavity leading to increased intracranial pressure (ICP) and reduction in cerebral perfusion pressure (CPP) [31]. Although these effects may be well tolerated by the uninjured brain, there is concern that ACS may contribute to secondary brain injury by its effect on CPP. Although not uniformly accepted as a therapy, there are some reports of head injured patients with elevated ICP, unresponsive to other measures for reduction of ICP, being treated by abdominal decompression [32,33].

Effects on the Integument

The effects of reduction in CO are particularly prominent in the integumentary blood flow. Profound reductions in flow to the abdominal wall have been observed. The reduction in integumentary flow may lead to problems with wound healing and higher risk of decubitus ulcers.

ACS, Systemic Inflammation, and Multiple Organ Dysfunction Syndrome

The large majority of patients that develop ACS are in a state of systemic inflammation and due to this are at a high risk for developing multiple organ dysfunction syndrome (MODS). The systemic inflammatory state in these patients is caused by (1) the primary pathology and its treatment causing ACS and (2) the tissue hypoperfusion and hypoxia caused by the cardiovascular and respiratory effects of ACS. Studies have clearly demonstrated an association of ACS and MODS [34]. What is less clear is whether MODS is caused or contributed to by ACS or whether the primary condition and its treatment that led to the development of ACS, independently caused MODS also. In animal models, ACS is associated with a disproportionate reduction in mesenteric flow, even when the mean pressure and CO are maintained [26]. In a human study of patients requiring high-volume resuscitation it was shown that patients resuscitated to a supraphysiologic oxygen delivery of 600 mL per minute per m^2 by volume loading required significantly larger volume as compared with a matched group resuscitated to only 500 mL per minute per m^2. As expected, the supraphysiologic group with the higher volume resuscitation had a higher incidence of ACS. The unexpected finding however was that the supraphysiologic group that developed ACS also had a higher incidence of gut ischemia, as measured by gastric mucosal pH, and worse outcomes [35]. The authors opined that the mesenteric ischemia, present despite higher systemic oxygen delivery in the supraphysiologic group, was caused by the ACS and was responsible for the worse outcomes. A large animal (swine) study examined the cytokine response to ACS alone, shock alone, or sequential shock resuscitation and ACS. It demonstrated that when ACS follows shock and resuscitation the cytokine response and neutrophil-mediated end organ injury are amplified as compared to either of the states occurring alone [36]. Another small animal study examined the effect of ACS at different time periods following shock and resuscitation. That study demonstrated that ACS was associated with worse outcomes in terms of end organ damage, and mortality when it occurred at the time when the neutrophils were maximally primed by the preceding shock and resuscitation [37]. Putting all of these studies together the hypothesis gaining acceptance is that the ACS acts as a second inflammatory stimulus—second hit in a two hit model—precipitating MODS in patients already primed by the primary condition that led to the development of ACS [38]. If this hypothesis is accepted, then the mechanism by which ACS acts as a second inflammatory stimulus needs further study. Some believe that increased bacterial translocation is the mechanism by which ACS acts as a second inflammatory stimulus leading to MODS. Some [28,39,40], though not all [41], animal studies of ACS have demonstrated increased bacterial translocation from the gut.

TECHNIQUE OF MEASURING IAP

A number of techniques have been used to measure IAP. Some are more invasive than others. IAP can be measured directly by accessing the peritoneal cavity. This method has been used during laparoscopic procedures, but is impractical due to the invasiveness and risk of infection outside of the operating room. Other techniques depend upon indirectly measuring IAP by measuring the pressure within the lumen of a hollow structure to which the IAP is directly transmitted—urinary bladder, stomach, rectum, or inferior vena cava. Of all the techniques, the most commonly used one is measuring pressure within the urinary bladder via a bladder catheter. The technique is simple and noninvasive since virtually all patients that may or do develop ACS have an indwelling bladder catheter. The setup

consists of a three-way stop cock connected to (1) the aspiration port of the urine collection bag tube via pressure tubing and an 18-gauge needle, (2) a 50-mL syringe with sterile saline, and (3) pressure transducer tubing. The actual technique consists of emptying the bladder, clamping the tube of the collection bag distal to the aspiration port, and instilling 50 mL of sterile saline into the bladder. After instillation of the saline, the clamp should be briefly loosened to empty the tubing toward the patient's side of air, and reapplied without loosing the saline. After emptying the air, the pressure within the bladder is measured and recorded. The level of the pubic symphysis is considered 0 mm Hg [8]. Studies have shown excellent correlation between the true IAP and the bladder pressure measured by this technique. Like all techniques however, the accuracy of the measured pressure depends on how meticulously it is performed. The greatest source of error comes from incomplete emptying of the air. Air in the system anywhere from the transducer through the three-way connection into the pressure tubing, urine collection bag tubing, and the bladder catheter can dampen the pressure and give an erroneously low reading. Also in patients with very small bladders or those having bladder spasms the pressure recording maybe falsely high. If the above sources of error are kept in mind and care taken to avoid them, bladder pressure measurement is an excellent technique of monitoring patients for ACS, and is by far the commonest one used for this purpose.

MONITORING FOR AND INCIDENCE AND PREVALENCE OF ACS IN THE ICU

Patients at risk of developing ACS may broadly be classified into five categories: (1) patients with severe systemic sepsis from any source, especially those where the source is within the abdomen; (2) patients undergoing massive fluid resuscitation for shock usually septic or traumatic, especially where the source of hemorrhage is within the abdomen; (3) patients undergoing abdominal damage control surgery; (4) patients with an intra-abdominal catastrophe, for example, severe pancreatitis, bowel necrosis, etc; and (5) patients undergoing large-volume resuscitation for major burn injuries. All such patients should be monitored for the development of ACS usually by intermittent bladder pressure measurements. It should be borne in mind that even patients that are being managed with the open abdomen technique for the prevention or treatment of ACS can develop recurrent ACS—tertiary ACS—and should be monitored for it. In addition, any critically ill patient with acute cardiorespiratory deterioration should be evaluated for the development of ACS.

The exact prevalence of ACS in the ICU population is difficult to determine since (1) it is different in differing patient populations, so if the ICU manages trauma, surgical and burn patients the incidence and prevalence will be higher as opposed to a medical ICU, with the mixed ICU falling somewhere in between and (2) differing definitions of IAP, IAH and ACS used by different investigators. In a prospective multicenter study examining the prevalence of IAH and ACS, where IAH was defined as IAP > 12 mm Hg, and ACS was defined as IAP > 20 mm Hg with at least one organ system failure, 59% of patients had IAH and 8% had ACS. As expected, the prevalence was higher in surgical, trauma and burn patients as compared to medical patients. Also in burn patients the development of ACS was correlated to the size of the burn [42]. Another multicenter study with similar definitions of IAH and ACS was conducted in fourteen ICUs. That study enrolled 250 consecutive patients and followed them to discharge, death, or for 28 days and recorded the cumulative incidence of IAH and ACS. The cumulative incidence for the period of study was 32% for IAH and 4% for ACS, although only one patient required decompression. In this later study however, medical patients that tend to have a lower incidence of ACS accounted for 46% of the study population. The same study also examined the risk factors for the development of IAH and also it's effect on outcomes. It concluded that the development of IAH was an independent predictor of mortality, and the independent predictors of IAH on day one were liver dysfunction, abdominal surgery, fluid resuscitation with > 3,500 mL over the preceding 24 hours, and ileus [43].

TREATMENT THRESHOLD

Although all agree that if a patient has severely elevated IAP with multiple organ system dysfunction, the patient should be treated for ACS. What is less clear is whether to treat patients much earlier in the process where the IAP is only moderately elevated and there is borderline dysfunction of only one organ system, or even earlier when the IAP is barely above 12 mm Hg. Since in the large majority of patients the treatment entails surgery and leaving the abdomen open, there are potential risks to the therapy. On the other hand there is evidence to suggest that earlier the treatment is initiated better is the final outcome [11,12,44]. In balance, all patients at risk of developing ACS should be monitored by frequent bladder pressure measurements. Patients that develop organ system dysfunction that, in the judgment of the treating physician, can be causally related to IAH should have therapy initiated. If the patient has increasing IAP but does not have any organ system dysfunction then the monitoring should continue with close observation for the development of organ system dysfunction, so that therapy can be initiated at the earliest sign of dysfunction. Finally almost all patients with IAP > 20 mm Hg and rising, even without evidence of organ system dysfunction, should have therapy for impending ACS.

TREATMENT OF ACS

Therapy for ACS or impending ACS is aimed at reducing IAP. In the large majority of patients, this entails surgical decompression by performance of a laparotomy, and leaving the abdomen open till the visceral swelling and/or the fluid accumulation within the abdomen is diminished to a point that the IAP will not rise to pathological levels on abdominal closure. As this is fairly radical therapy with significant morbidity less invasive medical therapy has been attempted.

Medical (Minimally Invasive) Management

Medical management of ACS has limited application at best. It is possible that with more study, medical management may become the modality of choice for the patients in the prodromal phase where there is impending organ system dysfunction. Medical therapy consists of one or more of (1) neuromuscular blockade; (2) needle/tube drainage of intra-abdominal fluid; and (3) continuous external negative pressure therapy by special custom made devices.

Neuromuscular blockade is attractive in theory but no studies have been performed to evaluate it as sole therapy for ACS. It is often used in situations where abdominal closure was desirable and hence was performed but due to many factors, the closure was "tight." Two case reports are available where neuromuscular blockade was used for the treatment of acute ACS. One report however cautioned that surgical decompression may still be necessary after treatment with neuromuscular-blocking agents [45,46]. Aside from these case reports no

studies are available that have adequately tested this form of therapy for acute ACS.

A small proportion of patients develop ACS not due to swelling of the viscera, rather due to accumulation of large volume of fluid and/or blood within the abdominal cavity. This is more often observed in patients with secondary ACS especially when caused by volume resuscitation for major burns. Such patients can be treated by placing a needle or small catheter within the peritoneal cavity. Case reports of successful management are present in the burn literature [47].

Continuous external negative pressure therapy is performed using custom made devices that surround the abdomen and create a negative pressure outside of the abdominal wall. Such devices have been used successfully in morbidly obese patients with chronic ACS [48,49]. There application in patients with acute ACS has not been reported, but in animal studies of acute ACS, they have shown potential [50].

Surgical Therapy

Surgical therapy in the form of decompressive laparotomy with the abdomen left open is the most often used treatment modality for impending or actual ACS. There is a large body of literature to support that such therapy, when performed early, rapidly reduces IAH and reverses organ system dysfunction. However, it should be pointed out that there have been no randomized trials to prove the benefits. The available evidence in favor of its use is class-II at best and is based on expert opinion and case control studies.

Surgical decompression of the abdomen for the treatment of ACS is performed by a generous midline laparotomy. After the laparotomy, the abdomen is left in the open state—fascia is not reapproximated. There are a number of methods available for managing the open abdomen. The method of management should be such that it can be performed rapidly, prevent heat loss from the internal viscera, protect the swollen viscera, and allow relatively free egress of the large amount of fluid that may accumulate within the cavity with continued resuscitation. In addition, the method should not damage the fascia and skin so that formal closure can be achieved later. In the authors' current practice, a large plastic sheet is laid over the bowel, and tucked deep in the paracolic gutters laterally, over the stomach/spleen and liver superiorly, and deep in the pelvis inferiorly. This sheet not only protects the internal viscera, and prevents heat loss, it also prevents adhesion formation between the bowel surface, and the abdominal wall, allowing for formal fascial closure at a later date. Small perforations are made in this sheet to allow fluid egress. Moistened gauze bandage is placed on top of this plastic sheet, and drains—Jackson Pratt or large (20 Fr) red rubber with multiple holes—are placed within the bandage. A Steridrape large enough to cover the bandage and adhere to the surrounding skin is placed over the bandage. The drains are connected, through collecting buckets, to wall suction at about 100 mm Hg. This system is easy to manage for the nursing staff, and allows for the fluid to be measured.

There are multiple problems associated with the open abdomen. In the absence of normal biological coverage, the body loses heat, the exposed viscera can desiccate, fistula can form from the mechanical trauma of dressing changes, and the large open wound is a major metabolic drain to the body. In addition to these short-term problems, in the longer term, in the absence of a complete fascio-muscular envelope, it is difficult to perform many physical actions for gainful employment. Because of these factors, how the open abdominal wound is managed has both long- and short-term consequences. There is no single method that will be suitable for all patients, and some tailoring to the need of the individual patient will be necessary to optimize functional outcome, and minimize complications.

Patients, in whom recovery progresses rapidly with brisk diuresis, and resolution of bowel edema, it may be possible to achieve fascial closure within 5 to 7 days. In many instances, however, this does not happen, or the patient develops some septic complication and the bowel becomes swollen again. After about a week in the open situation two factors prevent fascial closure. First, the fascial edges retract laterally, and second, adhesions form between the external surface of the bowel, and the abdominal wall. A plastic sheet interposed between the bowel surface and abdominal wall serves to prevent adhesion formation, and the VAC apparatus (KCI USA, Texas) can help medial mobilization of the retracted fascial edge. Using these techniques fascial reapproximation has been achieved up to 3 weeks after decompressive surgery [51].

Patients in whom, despite all measures, fascial closure is not possible, skin flaps can be mobilized, and closed over the bowel. In situations where skin flaps cannot be mobilized, the bowel surface can be allowed to granulate over, and then covered with split thickness skin graft. While waiting for adequate granulation tissue to form, extreme care is necessary, with minimum dressing changes performed very delicately so that mechanical trauma to the bowel surface is minimized, and fistula formation is prevented. After skin coverage is achieved, either by medial mobilization of skin flaps or by split thickness skin grafts over the granulated bowel, patients are left with a large ventral hernia that will require repair at a later date. The repair is usually carried out 6 to 9 months later to allow the inflammatory reaction to subside, and adhesions to become less vascular. A good way to check if a patient with split thickness skin graft is ready to have it taken off and hernia repaired is to try and pinch the skin off the bowel. In the initial stages, the skin graft is tightly adherent to the bowel wall, not allowing the skin to be pinched up. With the passage of time, and resolution of the inflammatory adhesions, the skin can be pinched off the bowel. Multiple techniques are used to repair the ventral hernia and reconstruct the abdominal wall. An innovative approach involves separating the various layers of the abdominal wall and instead of the patient having an incomplete multilayered abdominal wall the patient ends up with a single layered, but complete, fascio-muscular abdominal wall [52]. This approach allows native tissue to be used and avoids the need of prosthetic meshes, with their attendant complications. Good long-term functional results have been reported with this technique [53]. Alternatively, permanent prosthetic mesh may be used to bridge the gap in fascia, or a combination of techniques can be used. Preoperative use of tissue expanders to facilitate tension-free repair of these large ventral hernias has also been reported [54].

PREVENTION OF ACS

The best method of preventing the development of ACS is prompt recognition by frequent bladder pressure measurements and early action to prevent rising IAP turning into frank ACS with organ system dysfunction. In some surgical patients however, it may be possible to recognize that the patient has a high likelihood of developing ACS postoperatively. In such patients, surgeons are leaning toward preventing the development of ACS by leaving the abdomen in the open state. An interesting study was performed on patients with ruptured abdominal aortic aneurysms, in whom outcomes of patients with early placement of mesh (avoiding tight fascial reapproximation and possible ACS) were compared with outcomes from similar patients in whom tight closure was performed only later to be replaced by mesh due to the development of ACS. The incidence of multiorgan system failure was significantly lower in the patients where a tight closure and possible ACS were avoided [44]. In patients undergoing laparotomy and who fall

into the high-risk category for the development of ACS, strong consideration should be given to leave the abdomen open and prevent ACS.

The other major group of patients that is likely to develop ACS are those receiving large volume crystalloid resuscitation. Although early and rapid volume resuscitation is in many situations the only therapy that will rapidly reverse hypoperfusion, it is an independent risk factor for the development of ACS. Careful and frequent reevaluations should be performed on all patients receiving large volume resuscitation so that as soon as the need for the large volume diminishes, the infusion is turned down to minimize the chances of developing ACS [55].

OUTCOMES FOLLOWING ACS THERAPY

Patients requiring therapy for, or prevention from, ACS tend to be critically ill and have high morbidity and mortality. However, the development of ACS tends to increase mortality [34]. The reported mortality of patients requiring abdominal decompression for ACS is 29% to 62% [56]. In addition, patients with open abdomens pose significant management challenges if the morbidity of the treatment—open abdomen—is to be kept low. The most significant source of morbidity is the development of enterocutaneous fistula with rates reported as high as 18% [57]. To avoid this, dressing changes should be kept to a minimum and the exposed bowel should not be allowed to desiccate by placing nonadherent dressings over it. Besides this, the open abdomen is a significant metabolic drain to the body. This large open wound, coupled with the inflammation from the condition leading to the development of ACS, can rapidly lead to a state of severe malnutrition. Patients should be given adequate nutritional support, enteral if possible, and parenteral if not. By using evidence-based practices and continuously evolving clinical practice as knowledge becomes available, certain ICUs have shown a remarkable improvement in outcomes. Cheatham et al. in a recent study demonstrated that although the patient population remained the same, survival to hospital discharge improved from 50% to 72% and same admission primary fascial closure improved from 59% to 81% [58].

Despite improvements, the short-term in-hospital mortality and morbidity of patients managed with the open-abdomen technique for ACS remains high. However, patients that survive to discharge do surprisingly well. A prospective study examining the physical and mental states and employability of patients that had undergone management of ACS by the open-abdomen technique, demonstrated that within 18 months of abdomen closure, these indices were equivalent to a comparable cohort that did not have the open abdomen [59].

THE FUTURE

Despite the large body of literature about ACS, there are a significant number of intensivists and a small number of surgeons who continue to discount the existence of this disease entity. It is important to continue to educate these clinicians for the benefit of their patients. Further research needs to be carried out to define exactly which patients are likely to develop ACS so that prophylactic measures can be performed and ACS prevented. In addition, there needs to be a better understanding of the threshold at which therapy is the most beneficial so that only the patients that are likely to benefit from the therapy are subjected to the risks of the therapy. Finally, research in other modalities of resuscitation that can reduce the large volumes necessary will help in preventing ACS. A better understanding of the systemic inflammatory response with the attendant capillary leak may allow therapies to be developed that can attenuate the "runaway" systemic inflammation or at least reduce the capillary leak thereby reducing the chance of developing ACS.

CONCLUSION

Raised IAP leads to IAH that can cause organ system dysfunction and this combination of IAH and organ system dysfunction is termed ACS. There remain many areas of confusion in terms of terminology, diagnosis, appropriate treatment threshold, and the best treatment. The recent World Congress on ACS has helped clarify some of these issues. Any patient with organ system dysfunction or impending dysfunction in association with IAH should have prompt therapy. Although there are some medical therapies that show some promise, the best therapy to rapidly decrease IAP and reverse the organ system dysfunction remains surgical decompressive laparotomy and leaving the abdomen open. The open abdomen can be associated with significant morbidity hence extreme care is necessary in the management of such patients. As soon as the patient's condition improves attempts to close the abdomen or at least provide biological coverage should be initiated. In patients who are left with a large hernia, delayed repair with component separation or prosthetic mesh offers excellent long-term functional results.

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CHAPTER 153 ■ NECROTIZING SOFT TISSUE INFECTIONS

RICHARD L. GAMELLI AND JOSEPH A. POSLUSZNY JR

Necrotizing soft tissue infections (NSTIs) include a spectrum of diseases ranging from necrotizing fasciitis to gas gangrene and Fournier's gangrene. These infections occur within the soft tissue compartment from the dermis to the fascia and deep to the muscle layer, are associated with necrotizing changes, progress rapidly and can occur at any location in the body. Although many terms have been used to describe these infections, NSTI encompasses all necrotizing infections of the soft tissue compartment as they share common clinical, pathophysiologic, microbial, treatment, and outcome characteristics [1].

Most of the clinical information for NSTIs stems from large retrospective reviews [2–6]. Few prospective studies have

been performed given the high morbidity and mortality associated with these infections. However, these retrospective reviews have been surprisingly similar, each confirming previous data on risk factors, inciting events, microbiology, diagnosis, prognosis, and management while providing unique findings about their populations, NSTI, and its management.

EPIDEMIOLOGY AND RISK FACTORS

Surveillance of NSTIs in the United States no longer occurs, but the incidence can be estimated from epidemiologic studies [7]. Using a statewide database, Mulla et al. estimated an incidence of NSTI of 1.3/100,000 people with a total of 216 patients in Florida treated for NSTI in 2001 [8]. Demonstrating the frequent occurrence of cellulitis and rare incidence of NSTI, using an insurance claims database in Utah, Ellis Simonsen et al. estimated an incidence rate of cellulitis of 24.6/1,000 person years with an incidence rate for NSTI of only 0.04/1,000 person years [9]. NSTI is found in all age groups but most commonly in adults [10].

NSTIs occur in a wide range of patients who almost always possess preexisting conditions. More than 80% to 90% of patients with NSTIs possess comorbidities [2,3,11], whereas 62% may have three or more preexisting conditions [11]. Diabetes is the most frequent preexisting condition. In two large retrospective reviews, diabetes was present in 56% and 70% of the patients, respectively [2,4]. Other common preexisting conditions include obesity, hypertension, cirrhosis/chronic liver failure, peripheral vascular disease, HIV, and immunosuppressive therapy [2,3,12,13]. Behaviors like intravenous drug abuse (IVDA) and alcoholism leading to chronic liver disease also increase the risk of developing a NSTI [2,6,11,14]. Preexisting disease is not only a risk factor for NSTI but also for mortality [15]. When totaling comorbidities, patients who died had an average of 1.5 comorbidities versus 1.0 for survivors [3]. Preexisting conditions that correlated with mortality include cardiac disease, pulmonary disease, carcinoma, malnutrition, and IVDA [4].

Although preexisting conditions may increase the risk of developing a NSTI and mortality from NSTI, time to surgical debridement is the main risk factor for mortality. Since 1985, we have known that both prompt and radical surgical debridement of all devitalized tissue improves mortality [16]. Since then, many studies have supported early and aggressive surgical therapy for NSTI. Bilton et al. showed that delay in therapy increased mortality (38% mortality) when compared with early and aggressive surgical debridement (4% mortality) [12]. McHenry et al. found an average time to debridement of 25 hours in survivors but 90 hours for nonsurvivors [5]. Elliott et al. showed an average time to debridement of 1.2 days for survivors and 3.1 days for nonsurvivors [4]. On multivariate analysis, Wong et al. found that a delay in surgery of more than 24 hours was the only variable to correlate with increased mortality [2].

Although the incidence of NSTI is relatively low, the mortality is high at approximately 25% [17,18]. Early and radical surgical debridement is the key to successful treatment.

INCITING EVENTS

Many patients report an insect bite, blister, abscess, or the feeling of a pulled muscle several days prior to presenting with a NSTI. Although some (15% to 52%) cases of NSTI are idiopathic in origin, the remainder have an identifiable source [3,5,11,15]. Abscesses, foot ulcers, traumatic wounds, burns, surgical wounds, IVDA, decubitus ulcers, perforated viscus, and strangulated hernia were all identified as inciting events by Elliott et al. [4]. Endorf et al. also reported liposuction, an infected arteriovenous graft, invasive rectal cancer, a percutaneous gastrostomy tube site, and an enterocutaneous fistula as suspected causes of NSTI [3]. Anaya et al. found inciting events to include subcutaneous/IV injection, trauma, postoperative wound infection, boils, chronic wounds/ulcers, bites, and perirectal abscesses [11].

PATHOPHYSIOLOGY

Regardless of the inciting event, the pathophysiology of NSTIs is quite similar. NSTIs are a specific disease process in which entry of organisms through a compromised skin barrier results in a soft tissue infection that rapidly spreads along the superficial fascia of the subcutaneous tissue but initially spares the overlying skin and underlying muscle [19]. The rapidly spreading infection causes thrombosis of penetrating vessels, which in turn causes necrosis of overlying tissues supplied by those vessels. Histologic examination reveals necrosis of the superficial fascia, thrombosis and suppuration of veins traversing the fascia and microorganisms proliferating in the destroyed fascia [2]. Systemic spread of infection causes overwhelming sepsis or toxic shock syndrome if associated with streptococcal exotoxin of group A streptococcus (GAS) [20,21]. When muscle is involved early, the pathogen is commonly a clostridial species [22].

MICROBIOLOGY

The microbial causes of NSTIs can be polymicrobial or monomicrobial. The majority of NSTIs (53% to 85%) are polymicrobial [2,4,5]. Organisms in polymicrobial NSTIs include anaerobes and aerobes, Gram-positive and Gram-negatives and rarely fungi (< 5%) [3,4,5]. In Elliott et al., the organisms recovered from NSTIs included streptococci, staphylococci, enterococci, *E. coli, Proteus, Klebsiella, Enterobacter, Pseudomonas, Acinetobacter, Eikenella, Citrobacter,* peptostreptococci, *Bacteroides*, clostridia, and fungal species [23]. In a similar analysis, Wong et al. identified streptococcal species, staphylococcal species, enterococci, *Escherichia coli*, *Acinetobacter*, *Pseudomonas,* and *Klebsiella* as the most common isolates with *Bacteroides* being the most frequent anaerobe [2]. In Elliott et al., four or more organisms grew from the initial wound culture almost 50% of the time [4].

Monomicrobial NSTI occurs in approximately 15% to 29% of cases and over 50% of these monomicrobial NSTI are attributable to GAS [2,4,5]. Occasionally, monomicrobial NSTIs are caused by clostridia species [22], methicillin-resistant *Staphylococcus aureus* (MRSA) [24–28], and even group B streptococcus [20]. Tissue cultures have been found to not yield any organisms in 9% to 18% of debrided tissue samples [2,3]. In cases in which no organism is cultured and GAS is suspected, polymerase chain reaction can be used to amplify the streptococcal pyrogenic exotoxin B gene in tissue samples [29]. Although this may not be necessary for immediate management, it may aid in subsequent antibiotic therapy, prophylaxis of other close personal contacts, and for epidemiologic studies.

Attempts have been made to classify NSTIs based on microbial characteristics and to correlate the infectious organism to an inciting event, risk factor, or anatomic location [2,30,31]. Given the lack of uniformity and consistency in this classification system and the need to still treat all NSTIs initially

TABLE 153.1

MICROBIAL CLASSIFICATION OF NECROTIZING SOFT TISSUE INFECTIONS

Type I	Polymicrobial
Type II	Group A Streptococcus ± additional organisms
Type III	Unique and emerging pathogens (CA-MRSA, *Acinetobacter*, *Clostridia*, *Vibrio*)

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*.

with prompt diagnosis, early surgical debridement, broad-spectrum antimicrobials, adequate nutrition and critical care support, labeling an NSTI based on the type of organism present should be used only to guide later antimicrobial choice and for research purposes. Therefore, we supply a slightly modified table listing the historical classification of Type I (polymicrobial) and II (GAS ± additional organisms) NSTIs with an additional classification of Type III (community-acquired MRSA, *Acinetobacter*, *Clostridial*, and *Vibrio* species) to include emerging or unique pathogens which require consideration when NSTI is suspected (Table 153.1) [30,31]. These unique NSTI pathogens are discussed in more detail later. Although some classifications consider Type I to be polymicrobial and Type II to be monomicrobial, given the virulent nature and incidence of GAS, these infections remain as their own group.

DIAGNOSIS

The diagnosis of NSTI is not difficult when obvious signs of tissue necrosis are present. However, this is rare. Wong et al. found that only 14.6% of their patients eventually diagnosed with NSTI had the diagnosis of NSTI or a suspicion of NSTI on admission [2]. Most often, patients were diagnosed with cellulitis or an abscess. Hard clinical signs of NSTI (bullae, skin necrosis, crepitance, gas on radiograph) are present on admission for only 44% of patients with NSTI [14]. The difficulty with diagnosing NSTI is determining when NSTI is present before these obvious signs present as delay is detrimental to patient outcome. If distinguishing nonnecrotizing infection from NSTIs is not possible, then close monitoring of physical examination changes is required to avoid further progression of the disease process. Therefore, the majority of this section focuses the physical examination features common to NSTI and measures that can be employed to earlier diagnose NSTI and thus, prompt more expeditious treatment.

Physical Exam

Signs shared by both nonnecrotizing and necrotizing soft tissue infections include pain, erythema, induration, and swelling. The hard signs of NSTI which may help to differentiate it from nonnecrotizing infection include crepitus, blistering, and skin necrosis, all of which occur at later stages of the disease process. In Elliott et al., on admission, crepitus was present in 36% of patients, skin necrosis in 31% and blistering in 23% [4]. Similarly, Faucher et al. found an open wound in 39%, crepitus in 32%, and vesicles in 23% of patients on admission. However, symptoms common to nonnecrotizing and necrotizing soft tissue infections (pain 89%, edema 84% and erythema 74%) were predominant on admission [11]. If a patient presents with tenderness, erythema and warmth, the development of bullae may be the first sign leading to a higher suspicion of NSTI [2]. NSTI has also been described as having poorly defined and indistinct margins of tissue involvement, tenderness beyond the area of cutaneous involvement and pain out of proportion to physical findings [2,4]. In an attempt to earlier differentiate benign soft tissue infections from NSTI, Wang et al. developed a staging system for the progression of NSTI using only cutaneous manifestations. Stage 1 included tenderness to palpation beyond the apparent area of skin involvement, erythema, swelling, and calor. Stage 2 included blister or bullae formation and later, Stage 3 included crepitus, skin anesthesia, and skin necrosis with dusky coloration. By Day 4 of hospitalization, 68% of their patients with NSTI displayed Stage 3 cutaneous manifestations whereas only 5% did at time of admission. Although this system helps to describe the cutaneous manifestations of NSTI, absence of these cutaneous manifestations does not exclude NSTI [32]. Waiting for the presence of Stage 3 cutaneous manifestations may be detrimental to the patient.

Imaging

Plain radiography, ultrasound, CT and MRI have all been studied as adjuncts to physical exam in cases of suspected NSTI. Classically, air or gas between the muscle and soft tissue layer is diagnostic of NSTI and very often, clostridial NSTI. However, gas is found on x-ray in only a small percentage (16–19%) of cases [2,14]. The soft tissue changes seen with both complex cellulitis and NSTI are indistinguishable on plain radiograph. Therefore, plain radiography is only valuable in the rare cases in which air is present between the tissues. Ultrasound may benefit these patients in that it is quick, noninvasive and can be performed at the bedside. However, there are few studies on ultrasound use to distinguish NSTI from cellulitis [33,34]. Yen et al. showed that ultrasound had 88% sensitivity and 93% specificity for NSTI in a limb using diffuse thickening of the subcutaneous tissue accompanied by a layer of fluid accumulation more than 4 mm in depth along the deep fascial layer when compared with the contralateral limb [33]. Ultrasound is limited by the need for operator experience, the interpretation of the images, and its use in body areas aside from limbs. CT can be used as an adjunct to an equivocal physical exam. Similar to the findings on plain radiograph, gas in the subcutaneous tissues is characteristic of NSTI on CT. Since gas is not seen in all cases of NSTI, other features include thickened, asymmetrical fascia, fluid and gas collections along the deep fascial sheaths, and extension of edema into the intermuscular septa and muscles [35,36]. MRI has also been studied in the differentiation between NSTI and simple/complex cellulitis using fascial inflammatory changes as the indicator of NSTI [37,38]. MRI was found to have a sensitivity of 100% and specificity of 86% in a small cohort [37]. However, whether NSTI could have been diagnosed prior to MRI or if the delay needed for MRI altered patient outcome were not identified. If an imaging modality is deemed necessary to confirm NSTI due to equivocal physical examination findings, it may be prudent to start with the least invasive plain radiograph to look for gas and then progress to CT if necessary. Ultrasound can be used in centers if the technician and radiologist are comfortable with the exam and its interpretation. Operative debridement should not be delayed in cases in which NSTI can be confirmed on physical exam.

Laboratory

Laboratory values may aid physical examination in differentiating nonnecrotizing from necrotizing soft tissue infections.

Wall et al. used admission white blood cell count greater than 15.4×10^9 per L and serum sodium less than 135 mmol per L to help differentiate necrotizing infections from simple cellulitis [39]. Their model had a sensitivity of 90% and specificity of 76%. Positive predictive value was only 26%, but negative predictive value was 99%. This model was particularly effective in the absence of hard signs of NSTI. Wong et al. proposed another scoring system entitled the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) [40]. This model consists of point values assigned for C-reactive protein (above or below 150 mg per L), white cell count per mm^3 (less than 15, 15 to 25, or more than 25), hemoglobin (more than 13.5, 11 to 13.5, or less than 11), sodium (more or less than 135 mmol per L), creatinine (more or less than 141 µmol per L), and glucose (more or less than 10 mmol per L). With a possible total score of 13, they conclude that anyone with a score of 6 or greater should be carefully evaluated for NSTI, and a score of 8 or greater is highly predictive of NSTI (positive predictive value 93%). Careful physical examination and clinical suspicion should trump any score based on laboratory values, but these may be useful adjuncts in questionable cases.

Combined Diagnostic Modalities

Although adjunctive diagnostic modalities may help differentiate necrotizing from nonnecrotizing soft tissue infections, studies on their effectiveness are singular; little is known about the effectiveness of these modalities when combined [13]. In an attempt to combine physical exam and laboratory findings, Chan et al. prospectively studied the diagnosis and management decisions of surgery residents when presented patients with suspicion of NSTI using first only physical examination findings and then a combination of physical examination and serum WBC and Na values. Only 43% of patients had hard signs of NSTI on presentation. 90% of NSTI patients met one of these laboratory criteria (WBC count of > 15,400 and Na level of < 135) whereas 81% met both. Prior to knowing the laboratory values, residents felt that only 43% of patients had an NSTI. After reviewing these laboratory values and correlating their physical exam findings, suspicion of NSTI increased to 86%. Combining physical exam and radiographic data, Elliot et al. found crepitus, blistering or radiographic evidence of soft tissue gas in 85.3% of NSTI patients on admission [4]. Unfortunately, 20% of their NSTI patients did not have any of these three findings, leaving a large percentage of patients needing additional methods for diagnosing NSTI. As diagnosis of NSTI remains clinical, prospective trials incorporating multiple modalities for diagnosing NSTI will be essential to providing clinicians with a more reliable means of early diagnosis.

Others

Frozen-section biopsies have been effective in the diagnosis of NSTI. Again, the delay in waiting for pathologic review, the morbidity and high rate of negative tissue biopsies, and other logistical problems make frozen section somewhat unwieldy in the practical setting. Others have proposed a "finger test" consisting of a small incision under local anesthesia with digital probing. Lack of bleeding or presence of dishwater pus prompts exploration in the operating room [41]. Wang and Hung used tissue oxygen-saturation monitoring to diagnose NSTI [42]. In their series, a tissue oxygen saturation of less than 70% had a sensitivity of 100% and specificity of 97%. However, they excluded patients with peripheral vascular disease, venous stasis, shock, and hypoxia, while these subgroups may make up a significant portion of patients with NSTI.

Definitive Diagnosis

Histologic examination of involved tissue provides a definitive diagnosis but is not practical as infection may significantly progress during the time required for pathologic review. There are no consensus criteria for determining whether an infection is necrotizing in nature, but several common signs and symptoms are seen. Intraoperative findings of a NSTI include graying necrotic fascia, lack of resistance of muscular fascia to blunt dissection, lack of bleeding during dissection and the presence of foul-smelling dishwater pus [32].

SURGICAL MANAGEMENT

The mainstay of therapy for NSTI is surgery. Early surgical intervention has been shown to improve outcomes in patients with these infections [2,4,12,14,16]. The primary principle in operative debridement of NSTIs is expeditious removal of all necrotic or infected skin and subcutaneous tissue. Confirmatory findings include necrosis of the superficial fascia, thrombosis of superficial vessels, and foul-smelling discharge. There may be little or no resistance to blunt dissection along normally adherent superficial fascial planes [41]. Complete debridement of all necrotic tissue to areas of healthy, bleeding tissue is essential to allow delivery of antibiotics to the area as delivery cannot occur through the thrombosed vessels. Fluid and tissue cultures should be sent for immediate Gram's stain and aerobic and anaerobic culture and sensitivities. Deep fascia and muscle should be inspected; if muscle is involved, this may signal a clostridial infection. Dire circumstances necessitate amputation and can occur in 18% to 27% of cases [2,4,5]. Peripheral vascular disease and/or diabetes may predispose to amputation [2,5]. Colostomies may be necessary to temporarily control fecal flow in patients with large perineal defects [4] although it can be delayed if the infectious process is suspected to spread along the anterior abdominal wall.

Despite the obvious need for swift radical excision, incisions may be planned along geometric lines with an eye on eventual wound closure. Clearly viable skin should be preserved if possible to aid in future definitive wound coverage. Once hemostasis has been achieved, the wounds should be packed open, and a dilute Betadine solution in saline can be used for the initial dressing. Repeat debridements may be necessary, but it is preferable to attempt complete debridement at the initial setting to prevent further spread of infection. Large retrospective reviews have reported 2.7 to 3.8 debridements per patient [2–6]. Frequent wound examination is prudent, and any signs of ongoing spread of infection, including failure to respond to resuscitation, should prompt a return trip to the operating room for a second look. Bedside intervention may be necessary in the unstable patient and can be accomplished with sharp debridement and portable electrocautery.

Although prompt surgical management is key to decreasing morbidity and mortality, patients in septic shock on admission are an interesting challenge. The question is whether it is better to treat these patients with supportive care, antibiotics, and pressors and wait until hemodynamic stabilization for debridement or to continue resuscitation and supportive care while debriding the necrotic tissue. Boyer et al. showed that waiting > 14 hours for surgical treatment in patients with NSTI and septic shock significantly decreased survival [43].

Clearly, early surgical debridement of necrotic tissue is beneficial to patient outcomes. Easily identifying patients with an NSTI early in their course remains a clinical challenge, but relies on experienced physical exam and if needed, additional diagnostic modalities.

ANTIBIOTICS AND PHARMACOTHERAPY

Prompt empiric broad-spectrum antibiotic therapy is an important adjunct to operative debridement. Antibiotic choice should cover Gram-positive, Gram-negative, and anaerobic organisms. The most common antibiotic regimens consist of Gram-positive coverage with penicillin or an extended-spectrum penicillin derivative (or vancomycin in penicillin-allergic patients), Gram-negative coverage with aminoglycosides, cephalosporins or carbapenems, and anaerobic coverage with clindamycin or metronidazole [4]. The use of vancomycin, linezolid, daptomycin, or quinupristin/dalfopristin should be considered until MRSA has been ruled out [31,44]. Clindamycin has had particular success in the pediatric population [45] and may be of most benefit in blocking exotoxin and M protein production, leading to decreased tissue inflammation and sepsis [44,46]. The duration of antibiotic use has not been prospectively studied. Antibiotics should continue until at least all surgical debridement has taken place.

The use of intravenous immunoglobulin and activated protein C has been explored, but their usefulness remains undefined. Intravenous polyspecific immunoglobulin G has been used in combination with antibiotics in patients with accompanying toxic shock syndrome from invasive GAS infection [47]. Recombinant activated protein C/drotrecogin alpha has been used in critically ill patients with severe sepsis [48]. One case report identifies a potential benefit in the use of drotrecogin alpha in a patient with NSTI [44]. However, the use of drotrecogin alpha should be used with caution given the high risk of bleeding associated with its use combined with the typical need for repeated operative debridement and grafting.

Starting with broad-spectrum antibiotic coverage for Gram-positive, Gram-negative, and anaerobes with the addition of coverage for community-acquired (CA)-MRSA is essential. Once the pathogen(s) has been isolated, narrowing the antibiotic coverage is appropriate.

WOUND MANAGEMENT

After surgical debridement of NSTIs, patients may have extremely large soft tissue defects. Definitive wound coverage may require multiple modalities. Repetitive dressing changes should be used in the initial days following debridement until the wound is clean and there are no signs of recurrent or ongoing infection. Many surgeons advise saline wet-to-dry or wet-to-wet dressing changes. The use of 5% mafenide acetate solution applied to postgraft NSTI wounds has been shown to increase the success of first-time wound closure [49]. Additional topical antimicrobials that can be used include bacitracin, polymyxin, vancomycin, nystatin, and Betadine based on the culture and sensitivities of the pathogen [3].

A vacuum-assisted closure (VAC) device (Kinetic Concepts, Inc., San Antonio, TX) can be employed to reduce chronic edema, increase local blood flow, enhance the formation of granulation tissue, and promote contraction of the wound edges [50,51]. The VAC has also been useful in secondary wound infection after debridement of large areas of NSTI [52]. A small study by Huang et al. showed that a VAC may reduce wound size and decrease overall nursing care time, but was more expensive per day than conventional wet-to-dry dressings [53]. Any surrounding erythema, excessive pain or fevers should prompt removal of the VAC and examination of the wound. Regardless of the methods used, after the appearance of adequate granulation tissue, further surgical closure of the wound may be contemplated. In these often obese patients, redundant skin and subcutaneous tissue may allow for primary closure of the wounds, particularly in those involving the groin and perineal areas. Wounds not amenable to primary closure require coverage with split-thickness skin grafts and have been found to be necessary in 36% to 46% of patients [3,14].

The use of hyperbaric oxygen (HBO) has been advocated as a postsurgery adjunct in the treatment of NSTI as a means of decreasing morbidity, mortality and time to wound closure. However, a consensus on the benefit from HBO has not been established [4,54–56]. A recent retrospective review of hyperbaric oxygen therapy for NSTI showed a small, but not statistically significant decrease in mortality with HBO therapy [57]. A survival benefit may exist for the use of HBO in clostridial myonecrosis [4,56].

Following surgical debridement, operative wounds should be managed with frequent dressing changes with topical antimicrobial solutions until the area is free of infection and necrotic tissue. The use of a VAC device or HBO therapy may be employed based on a center's familiarity with these techniques.

NUTRITIONAL SUPPORT

These often critically ill patients will inevitably need nutritional supplementation to meet their increased metabolic state. Graves et al. found that 94% of their patients with necrotizing fasciitis needed either total enteral or parenteral nutrition for a mean of 24 days [58]. They used indirect calorimetry to determine individual energy requirements in this population, and found that these patients required caloric intake at 124% of their basal energy expenditure, or roughly 25 kcal per kg per actual weight per day. However, there were wide variations in energy requirements between patients, and they recommend routine indirect calorimetry to better provide appropriate nutritional supplementation.

Concomitant with ensuring adequate nutrition in patients recovering from an NSTI is proper glycemic control. Although no studies connecting poorer outcomes and hyperglycemia exist for patients with NSTIs, the depth of literature promoting the benefits of glycemic control in critical care can reasonably be extrapolated to the NSTI patient. Reduced morbidity and mortality in surgical ICU patients with tight glycemic control was first demonstrated in 2001 with the van den Berghe study [59]. Since then, control of blood glucose levels with algorithm or computer program assistance has become the standard of care in all ICUs [17]. Although preventing hyperglycemia is a priority so to is preventing hypoglycemia from overaggressive insulin use. Recently, the NICE-SUGAR study has demonstrated the side effects of hypoglycemic events with intensive insulin therapy; the safest and most beneficial glucose range has not yet been established [18]. Regardless, prevention of hyper- and hypoglycemia should improve patient outcomes. With the high prevalence of diabetes in patients with NSTI, glycemic control is an even more challenging task in this patient population.

OUTCOMES

Mortality

Mortality rates for NSTI range from 6% to 76% [5]. A recent review summarizing 67 outcome studies on NSTI since 1980 shows an average mortality of 23.5% [60], while another recent review reports a similar mortality rate of 25% [61]. As mentioned earlier, the greatest risk factor for mortality is time to surgical debridement [4,5,12,16,62]. In a more recent

examination of time to surgical debridement influencing outcome, Gunter et al. was able to reduce time from presentation to OR to 8.6 hours and thus decrease overall mortality to 9% by using an emergency general surgery service [63].

Various parameters have been used to predict mortality. In Yilmazlar et al., an APACHE II score of <13 was associated with a mortality of 21% while an APACHE II score of ≥ 14 was associated with an 86% mortality [57]. APACHE II scores of >20 have been associated with 100% mortality [57], and a 14.2-fold increased risk of death [62]. A LRINEC score of ≥ 6 was associated with increased amputation and mortality rates [64]. Bacteremia on admission has been associated with a 5.2-fold increased risk for death [19]. Preexisting conditions associated with higher mortality rates include IVDA, chronic renal insufficiency, and heart disease [62]. As expected, nonsurvivors have more body surface area involvement (13 vs. 6%), are obtunded (62%), have elevated serum lactate and creatinine on admission [4] and are older (age >60) [19].

Function, Disposition, and Cost

Given the high mortality rates associated with NSTI, the majority of studies focus on mortality outcomes. However, knowledge of functional outcome, hospital length of stay, and cost are important for the health care provider, patient, and families in terms of predicting physical, social, and economic support after recovery from the acute illness. Commonly, patients who survive an NSTI are left with a permanent physical disability. Retrospective reviews have shown that 15% to 28% [2,4,5,14,62] of patients with an NSTI will have an extremity amputated. Pham et al. retrospectively reviewed survivors of NSTI and found that, as expected, extremity involvement was associated with more functional limitations [65]. More long-term studies are necessary to assess the physical disability and therapy needs for these patients once their acute illness has resolved to properly maximize outcomes.

Almost half of all patients requiring radical surgical debridement will require further hospitalization or transfer to an inpatient rehabilitation facility after resolution of acute treatment [3]. Endorf et al. found the average length of hospital stay was 32 days for survivors and the overall ICU length of stay was 21 days [3]. Other studies report the average duration of hospitalization ranging from 29 to 41 days for all survivors [2,11].

Given the number of surgical interventions, length of hospital stay and use of critical care services, the cost of treating a patient with NSTI is quite high. Faucher et al. estimated a cost of $5,202 per patient day in 1999 for an average total of $153,803 per survivor [11]. Mulla et al. found that the median total patient charges for NSTI in 2001 were $54,533 [8]. With escalating health care costs both in and out of the hospital, an updated analysis of the long-term cost of NSTIs is necessary.

EMERGING PATHOGENS

Pathogens with unique antimicrobial resistance patterns and that specifically affect certain patient populations have recently been identified as causes of NSTIs. These pathogens should be considered when a patient is not improving despite adequate debridement and administration of broad-spectrum antibiotics.

MRSA

MRSA has been classified as either hospital-acquired (HA) or CA. Of NSTIs caused by MRSA, the majority of cases are CA [14,25–28]. The emergence of CA-MRSA may lie in its increased virulence and potential for necrosis. CA-MRSA manifests its virulence via Panton-Valentine leukocidin, a cytotoxin against leukocytes. These CA-MRSA infections are similar in presentation to other bacterial causes of NSTI. Unique inciting events or preexisting conditions leading to CA-MRSA susceptibility have not been identified. In a retrospective review, Lee et al. found MRSA in 39% of their NSTIs with at least 80% of these being CA-MRSA [27] Interestingly, 86% to 93% of CA-MRSA NSTI are monomicrobial [27,28]. Also, their antibiotic susceptibility profiles differ based on region. In Lee et al., from Houston, TX, they found that their MRSA were 100% susceptible to vancomycin or rifampin, 93% to trimethoprim-sulfamethoxazole, and 62% to clindamycin [27]. However, Miller et al. in Los Angeles, CA found their MRSA from NSTIs to be 100% susceptible to vancomycin, rifampin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole, 71% to tetracycline, 36% to levofloxacin, and 14% to erythromycin [28].

Acinetobacter

Acinetobacter baumannii as the cause for NSTI is rare but presents a clinical challenge in that it is resistant to most antibiotics, possesses unique virulence factors that may increase the speed at which necrosis occurs and is difficult to diagnosis given its pleomorphic appearance on Gram stain. *Acinetobacter* NSTIs are common in United States soldiers with wartime wounds sustained in Iraq and/or Afghanistan [66–68]. Antibiotic choice with an *Acinetobacter* infection may be the most challenging decision. In several case series and reports, *A. baumannii* strains were found to be sensitive to only amikacin, tobramycin, ampicillin/sulbactam [69], carbapenems [68], and possibly colistin [66,67] or were found to be resistant to all tested antibiotics [66,67,69]. Colistin should be used with caution due to its nephrotoxicity.

Clostridia

Clostridial myonecrosis, also known as "gas gangrene," is an aggressive infection of skeletal muscle. It is often associated with skeletal muscle trauma or recent surgery, but may be found with IVDA [70] and malignancy [22]. The most common organism seen is *Clostridium perfringens*, although it may be caused by *Clostridium novyi, Clostridium septicum, Clostridium histolyticum, Clostridium sordelli*, or *Clostridium fallax*. These organisms produce more than 12 toxins that may rapidly

TABLE 153.2

SUMMARY OF ADVANCES IN REDUCING MORBIDITY AND MORTALITY FROM NSTIs

- Early surgical debridement and management reduces morbidity and mortality [2,4,5,12,16].
- Laboratory values and imaging may help in the diagnosis of NSTIs when physical examination is equivocal [33–40].
- Empiric broad-spectrum antibiotics are critical adjunctive therapy [4,44–46].
- Prolonged nutritional support is needed for increased metabolic needs [58].
- CA-MRSA and *Acinetobacter* are new pathogens in NSTIs [14,25–28,57,64–66].

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; NSTIs, necrotizing soft tissue infections.

cause systemic shock. Symptoms may be similar to NSTI but gas in skeletal muscle or involved muscle at surgery can signal a clostridial infection. Antibiotic coverage is also similar, with penicillin, clindamycin, and metronidazole being the most common combination. Surgical exploration of superficial and deep muscle compartments is mandatory, and severe limb infection may require amputation [7]. Trunk involvement is associated with a worse outcome than limb infection (63% vs. 12% mortality) [71].

SUMMARY

NSTIs, albeit somewhat rare, can be rapidly lethal. The mainstays of management are prompt diagnosis, aggressive use of empiric antibiotics, and, most importantly, early radical debridement of affected tissue.

Advances in diagnosing and treating NSTIs are summarized in Table 153.2.

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CHAPTER 154 ■ ACUTE LIMB ISCHEMIA: ETIOLOGY, DIAGNOSIS, AND TREATMENT STRATEGIES

PEGGE M. HALANDRAS AND ROSS MILNER

INTRODUCTION

Acute limb ischemia (ALI) occurs in the setting of inadequate blood flow and therefore, oxygen delivery to an extremity. This state of hypoperfusion leads to systemic acid–base abnormalities and electrolyte disturbances that ultimately affect cardiopulmonary and renal function in patients managed in the intensive care unit (ICU). Revascularization of an ischemic limb leads to an additional host of metabolic problems as toxic byproducts that build up in the ischemic tissue bed and inflammatory mediators are released. ALI is a vascular emergency with 30-day mortality rates of 15% and amputation rates of 10% to 30% reported in the literature [1]. This chapter outlines common etiologies, diagnosis, and treatment strategies to manage acute lower extremity ischemia in patients that are often critically ill.

ETIOLOGY

The most common etiologies of ALI can be separated into two categories consisting of either embolism or thrombosis. Embolic events result from the detachment of thrombus or atherosclerotic plaques from proximal sources and often result in extreme peripheral ischemia as emboli may become lodged in a previously normal artery without significant collateral vasculature. Cardiac sources of emboli constitute 80% to 90% of peripheral emboli [2]. Myocardial infarction and cardiac arrhythmias such as atrial fibrillation lead to stasis and dilation of the left atrium and ventricle resulting in the formation of a cardiac thromboembolic source [3,4]. The presence of valvular heart disease and prosthetic heart valves are additional sources of cardiac emboli. Noncardiac sources of emboli include arterial aneurysms, ulcerated atherosclerotic plaque, and paradoxic emboli from venous thrombi. Additional noncardiac sources of emboli may occur with recent vascular interventions such as aortic surgery, percutaneous interventions with the passage of wires and catheters or balloon pump placement. The contribution of noncerebral emboli to the development of acute limb ischemia is illustrated by the observance that two-thirds of emboli travel to the lower extremity vasculature. One-half of these emboli obstruct iliofemoral arteries and the remaining half obstructs the popliteal and tibial vessels [5].

Thrombotic occlusions may occur in either native arteries or bypass grafts. Thrombosis of a native artery occurs with progression of an atherosclerotic lesion or rupture of an unstable plaque. Thrombotic occlusions occur most frequently at the site of arterial bifurcations or at areas of anatomic compression such as the superficial femoral artery at the level of the adductor canal [6]. Arterial trauma from fractures, dislocations, blunt injury, bullet wounds, or catheter access may result in pseudoaneurysms, intimal flaps, or dissections and may progress to acute thrombosis of a native artery. Femoral or popliteal aneurysms may also be responsible for ALI by either embolism of thrombus from the aneurysm or thrombosis of the aneurysm itself and occlusion of distal perfusion in the setting of inadequate collateral formation. More commonly,

thrombosis in situ occurs with occlusion of bypass grafts. Occlusion of a bypass graft in the immediate postoperative period is typically secondary to a technical defect. Occlusions of bypass grafts at later time periods may be due to intimal hyperplasia, progression of distal disease, low flow states experienced by critically ill patients, or acquired hypercoagulable states. In general, ALI secondary to thrombosis in situ or bypass graft occlusion may manifest as an acute-on-chronic process with less profound ischemia due to collateral formation not seen with acute embolic events. Therefore, management may not require immediate surgical revascularization and it is possible to proceed with initial nonoperative management including preoperative imaging such as angiography and thrombolytic therapy.

Other etiologies of ALI include aortic dissection creating malperfusion, intense vasospasm resulting from drugs such as cocaine, ergots or vasopressors, and hypercoagulable disorders. Alterations in coagulability have been attributed to both venous and arterial thromboembolism. Increases in coagulation activity in the arterial system in the ICU population have been observed in multitrauma victims, septic patients, and in the setting of heparin-induced thrombocytopenia (HIT) and disseminated intravascular coagulation (DIC) [7,8]. Likewise, inherited coagulation disorders are associated with arterial occlusions. Circulating antiphospholipids (lupus anticoagulant and anticardiolipin antibodies), gene mutations (prothrombin, factor V Leiden, methylene tetrahydrofolate reductase), alterations in activity levels of protein C and S, deficiencies of antithrombin III, and protein C&S have all been shown to contribute to the pathogenesis of arterial thrombosis [9].

EVALUATION

A careful history and physical examination is important in determining the etiology, establishing the extent of ischemia, and determining appropriate treatment of patients with acute lower extremity ischemia. Frequently, patients in the ICU are unable to provide valuable history regarding possible comorbidities that may contribute to the acute onset of their ischemia, coexistence of chronic arterial ischemia, and information concerning the onset of symptoms. Therefore, a careful review of the patient's medical history including a history of atrial fibrillation, coagulation disorders, recent percutaneous interventions, imaging demonstrating mural thrombus or aneurysmal disease, history of claudication or rest pain, and past lower extremity revascularization procedures should be performed. Risk factors including coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia and history of tobacco use should also be assessed.

A thorough physical examination is necessary to determine the duration and extent of ischemia that will ultimately determine the most suitable algorithm for treatment. Both lower extremities should be evaluated for signs of chronic disease including sparse hair growth, elevation pallor, dependent rubor, dystrophic nail growth, or chronic ulcers. Identifying the 6 "Ps" of acute ischemia including paresthesia, pain, pallor, pulselessness, poikilothermia, and paralysis is a useful tool to help establish the diagnosis and duration of acute ischemia. Initially, patients may experience pain in an ischemic limb that may progress to sensory deficit and eventually to paralysis. In addition, the level of pallor, coolness, or mottling may assist in determining the level of arterial injury of obstruction. Frequently, ischemic findings are most severe one joint distal to the level of obstruction.

A pulse exam may provide important clues about the underlying pathology but may also be misleading secondary to the subjectivity of this physical examination finding. Findings such as a "water-hammer" pulse indicating pulsation against an occlusion may be present following embolism or early thrombosis. A palpable thrill, audible bruit, or hematoma may indicate pseudoaneurysm or arteriovenous fistula in the setting of noniatrogenic or iatrogenic trauma seen with percutaneous interventions. If used correctly, continuous wave Doppler is a crucial tool in the bedside evaluation of the ischemic limb. A normal triphasic signal consists of forward systolic, reverse systolic and forward diastolic flow. A monophasic signal is characterized as a signal without pulsatile variability and signifies a proximal obstruction. Ankle–brachial indices (ABI) may also be obtained at the bedside and consist of calculating a ratio of ankle-to-brachial pressure. Abnormal results (< 0.9) must be interpreted with caution as medial calcification of vessels frequently observed in diabetics yield an ABI > 1. This occurs as calcifications prevent vessels from being compressed by a pneumatic cuff. ABIs may also be decreased at baseline in those patients with chronic lower extremity ischemia. Therefore, in a situation of suspected acute ischemia, ABIs should be compared between limbs and to ABIs obtained before the event if this value was recorded.

Further diagnostic testing may be required for operative planning but institution limitations and the urgency of revascularization should be considered when obtaining additional tests. Arterial duplex ultrasound is valuable for determining occlusive lesions, bypass graft occlusions, and the presence of distal and proximal arterial disease. This noninvasive test is operator dependent but has been shown to correlate with contrast angiography findings [10]. Digital subtraction angiography is considered the gold standard for diagnostic imaging in the acute setting. This testing modality provides anatomical detail concerning the offending lesion, presence of chronic atherosclerotic disease, and the status of distal arterial targets. Findings will assist in planning operative intervention including thrombectomy, bypass, or further percutaneous intervention. In addition to its diagnostic advantages, angiography may also be used as a therapeutic modality with the institution of catheter directed therapies. Adverse effects of contrast angiography include nephrotoxicity from contrast administration, embolization, and access site complications including dissection, pseudoaneurysm, arteriovenous fistula, and bleeding. Further imaging with CT or MRI may be necessary if aortic dissection or aortoiliac occlusion is suspected. Otherwise, these tests are time consuming and may not supply information regarding distal arterial runoff that cannot be obtained by angiography in the patient requiring urgent revascularization.

TREATMENT

Planning revascularization of the acutely ischemic limb requires consideration of the patient's overall medical condition, likely etiology and the viability of the ischemic limb. If the patient is not medically stable to proceed to the operating room or angiography suite, revascularization may be postponed in the interest of preserving "life over limb." In addition, revascularization of an ischemic limb with permanent ischemic nerve or muscle damage may result in a nonfunctional limb and primary amputation may be the most effective treatment strategy. Predicting the urgency of revascularization required to salvage an acutely ischemic limb is a difficult task and treatment paradigms have evolved with the advent of catheter directed thrombolytic therapy. The goal of the revised Rutherford Criteria proposed by The Society for Vascular Surgery and International Society for Cardiovascular Surgery (SVS/ISCVS) is to stratify levels of severity of ALI (Table 154.1). Category I limbs are considered viable with no sensory or muscle deficits. This category includes limbs that are not immediately threatened and may be managed either without an intervention or after a thorough evaluation. Class II limbs have been stratified into two subcategories. Class IIa limbs are marginally threatened

TABLE 154.1

CLINICAL CATEGORIES OF ACUTE LIMB ISCHEMIA

Category	Description/prognosis	Sensory loss	Muscle weakness	Doppler signal (arterial)	Doppler signal (venous)
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or None	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound paralysis (rigor)	Inaudible	Inaudible

Modified from reporting criteria recommended by the Society for Vascular Surgery and the International Society for Cardiovascular Surgery [11], Vascular Surgery, and the NORTH American Chapter.

with minimal sensory loss. This category of ischemic limbs can be salvaged with appropriate revascularization directed by further studies such as angiography. Class IIb limbs are immediately threatened with more profound sensory loss and mild-to-moderate muscle weakness. Salvage of Class IIb limbs should be managed with emergent revascularization efforts [11].

The main treatment modalities of acute limb ischemia include anticoagulation, open surgical management, percutaneous intervention, and primary amputation. A combination of both open surgery and percutaneous management are often required. Once the decision to proceed to either the operating room or angiography suite has been made, the patient should be systemically heparinized if no contraindications to anticoagulation exist. Full intravenous anticoagulation with heparin prevents further propagation of thrombus and recurrent emboli until definitive management is instituted [5]. Heparin bolus should routinely be 100 to 150 U per kg and a drip of 60 to 80 U per kg per hour should be started to achieve an activated partial clotting of greater than two times control.

Surgical Revascularization

Open surgical treatment includes Fogarty balloon thromboembolectomy, endarterectomy with patch angioplasty, and surgical bypass. If the diagnosis of an embolus to the femoral bifurcation is suspected, patients may be expediently managed by the passage of thromboembolectomy catheters via a groin incision in a retrograde and antegrade fashion. Femoral artery exposure may suffice but exposure of the below-knee trifurcation vessels may also be needed for adequate tibial–peroneal thrombectomy. Preoperative testing such as angiography or other imaging studies may be bypassed to avoid prolonged ischemic time. Focal femoral artery occlusions have become more common with frequent percutaneous interventions and the subsequent use of arterial closure devices. This complication can also be effectively managed by open surgical techniques such as foreign body removal, thromboembolectomy, endarterectomy with patch angioplasty, or interposition bypass. If after thrombectomy, an occluded outflow signal is detected or there is an absent pedal signal, an intraoperative arteriogram should be performed to identify native arterial lesions or residual thrombus. If the arteriogram reveals adequate inflow and distal target, and an appropriate conduit is available, surgical bypass may be the most appropriate option for revascularization. Long segment occlusions and thrombosed popliteal aneurysms with patent distal targets are indications for proceeding with surgical bypass.

Thrombolysis

Catheter-directed thrombolytic therapy has emerged as an alternative to open surgical treatment for ALI. Patients with Rutherford category I and IIa ischemia or with a high likelihood of thrombosis (in situ or bypass graft in the setting of inadequate conduit) are candidates for thrombolysis. Therapy includes performing an arteriogram to identify an acute occlusion and percutaneously crossing the lesion with a guidewire. Thrombus is then infused with thrombolytic agents through an infusion catheter. Infusion catheters typically allow for saturation of the entire thrombus with a lytic agent through a multi-sideport design or infusion guidewire. The effectiveness of thrombolytic therapy is typically monitored by reimaging with angiography at 6- to 12-hour intervals after initiation. Patients should also undergo serial neurologic, vascular and laboratory examinations. CBCs and fibrinogen levels should be followed to identify hemorrhagic trends and because fibrinogen levels less than 100 mg per dL have been associated with systemic fibrinolysis and an increased risk of bleeding, including intracranial hemorrhage [12]. Restoration of flow within a thrombosed artery or bypass graft will assist with unmasking the causative lesion and assist in planning future interventions to maintain patency. Percutaneous interventions may include angioplasty or stenting of native or anastomotic stenoses and open surgical interventions may include a new surgical bypass or surgical bypass revision.

Common thrombolytic agents used include streptokinase (produced by cultures of β-hemolytic streptococci), urokinase (extracted from human urine), and recombinant tissue-type plasminogen activator (rt-PA). Currently, there is no consensus regarding the superiority of one agent in terms of efficacy and safety. One open trial comparing intra-arterial streptokinase with intra-arterial and intravenous rt-PA confirmed 100% angiographic success with intra-arterial rt-PA as compared with intra-arterial streptokinase (80%) and intravenous rt-PA (45%). Thirty-day limb salvage rates were 80%, 60%, and 45%, respectively [13]. In contrast, a randomized trial comparing rt-PA to urokinase (UK) confirmed a faster 24-hour lysis rate with rt-PA but similar 30-day clinical success rates [14]. A secondary end point of the randomized Surgery versus Thrombolysis for Ischemia of the Lower

Extremity (STILE) study compared patency rates and safety between rt-PA and UK. No difference in efficacy or bleeding complications was reported between the two treatment groups [12]. In contrast, a randomized study treating thrombotic infrainguinal arterial occlusions with either UK or rt-PA showed slightly improved lysis in the rt-PA group with an increase in the rate of local hematomas [15]. A newer alternative is the concurrent use of abciximab, the platelet glycoprotein IIb–IIIa antagonist, with UK. A randomized trial in which patients received UK plus abciximab versus UK plus placebo showed a trend toward amputation-free survival at 90-days in the combination group as compared to the placebo group. Thrombolysis occurred at a faster rate but a higher risk of nonfatal major bleeding was seen in the combination group [16].

Several multicenter randomized control trials have compared open surgical revascularization with catheter directed thrombolysis. The Thrombolysis or Peripheral Arterial Surgery (TOPAS) study randomized patients with acute arterial obstruction (less than or equal to 14 days) to catheter-directed intra-arterial thrombolysis with UK or bypass surgery. Patients had both embolic and thrombotic etiologies including occluded bypass grafts. There were no significant differences between the two groups with regards to amputation-free survival at 6 months and mortality rates at discharge, 6 months and a year after randomization. At 6 months, the thrombolysis group underwent fewer open surgical procedures without a significant increased risk of amputation or death when compared to the surgical group [17]. The STILE trial randomized patients with nonembolic native artery or bypass occlusions (bypass within the past 6 months) to either treatment group. Composite outcomes of death, major amputation, and ongoing or recurrent ischemia were higher in the thrombolysis versus surgery group (61.7% vs. 36.1%). A secondary stratification of patients with regards to duration of ischemia confirmed that in patients with acute ischemia of < 14 days, amputation-free survival at 6 months and shorter hospital stays were improved in those patients treated with thrombolysis [12]. In summary, the findings in these trials are difficult to generalize as different etiologies (embolism, thrombosis, and occluded bypass grafts), different durations of pretreatment ischemia and different thrombolytic agents were analyzed. Therefore, a working party reached a consensus proposal on the use of thrombolysis in the management of lower-limb arterial occlusion [18]. Recommendations included the following:

1. Thrombolysis followed by correction of the causative lesion in patients with native artery occlusions with ischemia < 14 days is recommended. Immediate surgical revascularization should be a priority if thrombolysis will lead to an unacceptable delay in reperfusion.
2. Primary amputation is indicated in patients with irreversible ischemia.
3. Occluded bypass grafts may be managed by thrombectomy and surgical revision, catheter-directed thrombolysis, or insertion of a new graft. The age and type of bypass, duration, and degree of ischemia and availability of venous conduit should be considered when deciding on a treatment strategy.

Advances in percutaneous treatment of ALI include the adjuncts of mechanical thrombectomy and aspiration thrombectomy. These treatment modalities may be used alone in patients with contraindications to thrombolytic therapy, to debulk occlusive thrombus and thereby reduce the time needed for effective thrombolysis, or to remove residual thrombus following thrombolysis. Mechanical thrombectomy is performed with two FDA-approved devices in the infrainguinal arterial system. AngioJet relies on the Venturi effect in which saline is directed at high pressure in a retrograde fashion within the inflow lumen of the thrombectomy catheter. This creates a negative pressure zone at the tip of the catheter and results in thrombus fragmentation and aspiration. A pulse-spray of thrombolytic agent within the thrombus followed by mechanical thrombectomy, termed pharmacomechanical thrombolysis, is an additional treatment strategy employed with the AngioJet system. The Trellis Thrombectomy System is an additional mechanical thrombectomy device. This device allows isolation of a treatment segment by proximal and distal occlusion balloons. A dispersion catheter infuses thrombolytic agent within the treatment zone and an oscillating dispersion wire exposes the thrombus to the agent and fragments the thrombus. The fragmented thrombus is then aspirated via a port distal to the proximal balloon. Finally, mechanical thrombectomy may also be achieved with the use of percutaneous aspiration thrombectomy catheters. This technique involves a large-bore catheter connected to a syringe to aspirate thrombus.

TABLE 154.2

ABSOLUTE AND RELATIVE CONTRAINDICATIONS TO TREATMENT WITH THROMBOLYTIC THERAPY

Contraindications to thrombolytic therapy

Absolute
1. Established cerebrovascular event (including TIAs within last 2 months)
2. Active bleeding diathesis
3. Recent gastrointestinal bleeding (< 10 days)
4. Neurosurgery (intracranial, spinal) within last 3 months
5. Intracranial trauma within last 3 months

Relative major
1. Cardiopulmonary resuscitation with last 10 days
2. Major nonvascular surgery or trauma within last 10 days
3. Uncontrolled hypertension: > 180 mm Hg systolic or > 110 mm Hg diastolic
4. Puncture of noncompressible vessel
5. Intracranial tumor
6. Recent eye surgery

Relative minor
1. Hepatic failure, particularly those with coagulopathy
2. Bacterial endocarditis
3. Pregnancy
4. Diabetic hemorrhagic retinopathy

Modified from Working Party on Thrombolysis in the Management of Limb Ischemia: Thrombolysis in the management of lower limb peripheral arterial occlusion—consensus document. *J Vasc Interv Radiol* 7:S337–S349, 2003.

Contraindications to management of ALI with thrombolysis include category IIb ischemic limbs requiring immediate revascularization or category III ischemic limbs best treated with primary amputation. Contraindications to the use of thrombolytic agents are patients with a hemorrhagic disorder or an anatomic lesion with the potential to cause hemorrhage [18]. Table 154.2 lists both absolute and relative contraindications to thrombolytic therapy. Intracranial hemorrhage is one of the most devastating complications of thrombolytic therapy and may be fatal in some instances.

Finally, revascularization of an acutely ischemic limb may create significant tissue edema. The ischemia-reperfusion theory of cellular injury proposes that reperfusion of ischemic muscle results in multiple events causing cellular swelling and the formation of excessive interstitial fluid. This creates an environment in which extravascular pressure exceeds capillary pressure within a confined muscle compartment. Consequently, nutrient blood flow is restricted and will ultimately result in tissue infarction [19]. Therefore, four-compartment fasciotomy to prevent compartmental hypertension and further morbidity

may be necessary. The decision to perform a fasciotomy is frequently clinically based but may also be objectively guided by the measurement of compartment pressures.

CONCLUSION

In summary, ALI is associated with significant morbidity and mortality. ALI has multiple etiologies with the most common being embolism and thrombosis. Effective management demands that a clinician critically evaluate a patient to determine the patient's overall medical condition, contributing comorbidities and degree of ischemia. Careful physical examination will reveal clues regarding an acute embolic event in the setting of healthy lower extremity vasculature versus acute ischemia in the setting of chronic lower extremity ischemia. Open thromboembolectomy may offer the most expedient and effective revascularization of an acute embolic ischemic event. In contrast, catheter-directed thrombolytic therapy provides a mechanism for clearance of thrombus from distal runoff and unmasking of lesions responsible for an ischemic event. Correction of responsible lesions may proceed with percutaneous or open management. In general, revascularization with thrombolysis requires a longer time to revascularization and patients that have a contraindication to thrombolytic therapy may be excluded. Therefore, the management of ALI is most successful with a logical protocol that allows for the institution of multiple treatment modalities.

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CHAPTER 155 ■ PRESSURE SORES: PREVENTION AND TREATMENT

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PATHOPHYSIOLOGY

Pressure sores develop secondary to unrelieved pressure exerted on soft tissue overlying bony prominences. The National Pressure Ulcer Advisory Panel defines pressure ulcers as localized areas of tissue necrosis that develop when soft tissue is compressed between a bony prominence and an external surface for a prolonged period of time [1]. Clinicians frequently use the terms *decubitus ulcer* and *pressure sore* interchangeably. The word *decubitus* has its origin from the Latin word decumbre, which means to lie down [2]. The term decubitus ulcer therefore only applies to ulcers that occur in a lying position; it fails to describe ulcers that may occur in seated or other positions. Pressure sore is the preferred term because it describes all ulcers that result from pressure over weight-bearing areas regardless of position.

Landis [3] in 1930 suggested that constant pressure greater than the normal arterial capillary pressure, 32 mm Hg, can impair local perfusion. This is the most important determinant

in the development of pressure sores. The distribution of pressure in healthy patients in supine, prone, and various sitting positions has been extensively documented by various authors [4,5]. It is well accepted that the sacrum, buttocks, heels, and occiput are subject to the highest pressures in the supine position, with a range of 40 to 60 mm Hg. In the sitting position, pressures in excess of 75 mm Hg have been recorded over the ischial tuberosities [6]. The majority of pressure sores occur below the umbilicus, two-thirds in the hip and buttock region, and one-fourth to one-third in the lower extremities.

Studies of pressure tolerance in various tissue types by Husain [7] have demonstrated that muscle has a lower pressure tolerance when compared with skin and subcutaneous tissue. Le et al. [8] demonstrated that pressure applied to the soft tissue over bony prominences can cause infarction of muscle and subcutaneous tissue without skin necrosis. This explains the "tip of the iceberg" phenomenon not infrequently seen in clinical pressure sores. One of the most important studies regarding pressure tolerance was performed by Kosiak [9]. He demonstrated irreversible changes in dog muscle and skin when subjected to a pressure of 70 mm Hg applied continuously for 2 hours. More importantly, he showed that no changes occurred if pressure was relieved every 5 minutes. These findings illustrate the mechanism of pressure sore formation as well as reveal the major key to prevention.

There are multiple additional factors that contribute to the formation of pressure sores outside the local effects of unrelieved pressure. As suggested by the multifactorial hypothesis of Enis and Sarmiento [10], the intrinsic factors of malnutrition, advanced age, hypotension, impaired mobility, impaired sensation, and sepsis predispose critically ill patients to the development of pressure sores. Skin contamination with stool, excess moisture, and shear forces are extrinsic factors that further increase the risk of pressure sore formation.

EPIDEMIOLOGY

In the early twentieth century, pressure sores were most commonly observed in young patients with chronic diseases such as tuberculosis, osteomyelitis, and chronic renal disease. This changed in the mid-1940s with improved early and late mortality rates after spinal cord injury. Spinal cord injury patients became the largest high-risk group for the development of pressure sores. Today, the elderly citizens have become the fastest growing segment in the American population. Residents in nursing homes and chronic care facilities are now recognized as the largest high-risk group for the development of pressure sores.

In an acute care hospital, the prevalence of pressure sores ranges from 3% to 11% of all admissions. It increases to 28% when subpopulations of high-risk patients are studied. The average cost of treating an established pressure ulcer ranges from $4,000 to $40,000. This does not include medicolegal liability costs, which are an increasing concern and focus.

Patients in the intensive care unit (ICU) often have multiple risk factors for the development of pressure sores: restricted mobility, impaired sensation and/or mental status, impaired perfusion, fecal and urinary incontinence, poor nutrition, advanced age, shear forces, and friction. In addition, ICU patients have various other physiologic impairments. A study by Eachempati et al. [11] has revealed emergent admission, age, days in bed, and days without nutrition as independent predictors of pressure sore formation. Even more recently, Feuchtinger et al. [12] have found in the cardiac surgery population temperature manipulation, vasoactive agents, hypotensive periods, anemia, operating room time, steroids, and low albumin levels to be significant risk factors for the development of pressure sores. Diabetes mellitus and high acute physiology and chronic health evaluation (APACHE II) scores also identify high-risk patients [13]. Spinal cord injury patients continue to be a challenging subgroup. Improved awareness of the risk factors as well as knowledge of the options for prevention and treatment of pressure sores will improve patient care and allow for more efficient use of healthcare resources. Once pressure sores develop. There are few patients who will be candidates for definitive surgical closure because of their concurrent medical disabilities. The pressure sore then becomes a costly chronic medical problem. In any debilitated patient population, pressure sores are extremely difficult to heal.

RISK, EVALUATION, AND PREVENTION

Prevention of pressure sores in the ICU begins with education of the entire hospital staff. Identification of patients at high risk is the initial step. All patients should be routinely screened on admission for risk factors that may predispose them to the development of pressure sores. The basic tenets of prevention include pressure reduction over bony prominences, alternation of weight-bearing surfaces, good skin hygiene, and the maintenance or restoration of adequate nutrition. At this time, there is no universally accepted screening tool for quantifying risk for pressure sore development, but the risk factors are well known. Considering the cost of managing an established pressure sore, it is likely that excess prevention is less costly than nonaction. The Braden scale is one of the most widely used risk assessment tools. It has six subscales: sensory perception, skin moisture, activity, mobility, friction and shear, and nutritional status. Regardless of the screening tool, the most important factor is starting preventive measures as soon as patients at risk are identified [14]. Inattention to previously noted risk factors or early signs of skin breakdown can result in a clinically significant pressure sore in less time than the standard 8-hour nursing shift.

Dispersion of pressure is a vital component of preventive measures and management. Before the 1960s, frequent patient body positioning for avoidance of skin maceration was the mainstay of pressure sore prevention. This is still considered the basic tenet in preventive measure. Patients confined to bed should be turned every 2 hours. Alternating 30-degree oblique supine positions are best [15]. The 90-degree lateral position should be avoided. More importantly, patients in a sitting position should have their weight shifted several times every hour [6].

In the 1960s, pressure-reduction technology using the principle of dispersion became available to improve local blood flow and minimize tissue ischemia. These devices are based on the concept of suspension or buoyancy [16]. The greater the body surface area supported by the surface, the greater the distribution of the patient's weight against the mattress and the lower the effective contact pressure on the skin. The available devices achieve buoyancy through the use of water, air, gel, foam, or circulating ceramic beads. The cost of these various systems ranges from $35 to $140 per day of use.

It has been well demonstrated in the literature that transcutaneous oxygen tension can be maintained in an acceptable range in the supine position with the use of air-fluidized and low-air–loss beds in comparison to standard hospital mattresses [17]. Only with the use of air-fluidized systems is this maintained in the lateral decubitus position. Inman et al. [18] studied 100 consecutive patients who were at risk for pressure ulcer development and randomly assigned half to receive care on a standard ICU bed and half to a low-air–loss surface.

The patient groups were comparable, and all other treatment measures were standardized. The low-air–loss patient group developed fewer and less severe pressure ulcers than those who were treated on the standard surface. Taking into account the cost of the low-air–loss surface and the treatment of an established pressure sore, low-air–loss therapy is not only effective in preventing pressure sores from occurring, but it is also cost-effective. The low-air–loss mattress is a highly valuable preventive measure for the critically ill patient while not interfering with the patient's care.

Good skin care is another important adjunctive component of pressure sore prevention. This involves keeping the bed free of particulate matter and solid objects that may cause abrasions or lacerations. Daily skin assessments should be a part of routine nursing care to screen for the development of pressure sores, especially heel ulcers. Daily application of creams and lotions to the feet is inexpensive and can be vital to heel ulcer prevention. Control of both urinary and fecal incontinence and diarrhea are also important. As discussed previously, excess moisture may increase the possibility of pressure sore formation. Bacterial contamination can delay wound healing and extend the zone of tissue necrosis. Enterostomal therapists or wound care nurses can be invaluable resources in the management of these wounds. Colostomies are occasionally necessary to obtain control of the fecal stream with complex sacral or perineal wounds and open pelvic fractures. This decision should be made in conjunction with plastic and general surgical consultation.

Heel ulcers are a clinical problem that warrants special attention. A national pressure ulcer prevalence study by Meehan [19] identified the heel as the second most common site for the development of pressure ulcers. With the introduction of pressure-reduction surfaces, the incidence of sacral ulcers decreased, but there was a concomitant increase in heel ulcers. A study by Blaszczyk et al. [20] developed a useful heel pressure ulcer risk assessment tool to identify patients at risk for the development of heel ulcers.

The patient specific variables include; age over 70 years, diabetes mellitus, mental status changes (agitation, confusion, stupor, unresponsiveness), and immobility of the lower extremity. These specific risk factors are added up and the activity level is then assessed; this determines the risk factor level. Ambulatory patients should get universal heel precautions only. Patients who walk with assistance with one or no risk factors receive universal precautions only, two risk factors yield preventive precautions, and three or more risk factors yield strict precautions. Nonambulatory patients without any risk factors receive universal precautions, one risk factor yields preventive precautions, and patients with two or more risk factors receive strict precautions [20].

Universal heel precautions include daily assessment of feet, daily skin care (creams or lotions), turning every 2 hours, standard hospital pressure-reduction mattress, mobilization out of bed three times a day, and active range of motion. Preventive heel precautions additionally include assessment of feet two times a day, friction reduction (creams or lotions twice daily, socks or support hose, transparent films, or hydrocolloid to heels every week), and pressure reduction (pillow support keeping heels off bed, heel roll or heel cushion, passive range of motion exercises). Strict heel precautions additionally include foot assessment three times a day, creams or lotions three times a day, and heel protection (heel lift, heel cushion). This protocol resulted in a decrease of heel pressure ulcers in the medical ICU patient population [20].

Prior to surgical intervention for heel ulcers, including debridement, patients should be evaluated for vascular insufficiency by obtaining an ankle–brachial pressure index. If this is abnormal, a formal vascular surgery consultation should be obtained.

An effort should be made to remove trauma patients from spine boards and also remove rigid cervical collars as quickly as possible. Patients who require a cervical collar for an extended period should be assessed so that the collar fits properly. Blaylock [21] reported a successful routine for care that significantly reduced pressure ulceration from cervical collars. In patients with an unstable cervical spine, an oscillating support surface may reduce the risk of developing pressure sores. These low-air-loss mattresses also oscillate continuously from side-to-side up to 62 degrees to redistribute pressure on the skin. Selection of this surface should be made after consultation with a spine surgeon.

Nutritional assessment and support are obvious integral components in the care of every critically ill patient. It is well known that malnutrition impairs wound healing. A serum albumin less than 2.5 g per dL has been correlated with the development of pressure sores. It is important that a patient's nutritional status is optimized prior to any reconstructive surgical intervention needed to close a chronic pressure sore. Weekly monitoring of the visceral protein prealbumin can be used to assess the adequacy of the patient's nutritional status and response to dietary supplementation. A more detailed discussion of nutritional assessment and management is beyond the scope of this chapter.

Other patient specific issues to consider are anemia of chronic disease, spasticity in spinal cord injury patients, and long-standing contractures.

WOUND CLASSIFICATION AND MANAGEMENT

According to the National Pressure Ulcer Advisory Panel, wounds are generally classified as follows [1]:

Grade I: Nonblanchable erythema of the skin with the lesion being limited to the epidermis and dermis. Heralds skin ulceration. (Persistent skin erythema.)

Grade II: Any partial-thickness skin loss. Full-thickness ulceration of the skin extending through to the subcutaneous adipose tissue at any level above muscle fascia. (Ranges from abrasion, blister to shallow crater clinically.)

Grade III: Ulceration extending down through the subcutaneous tissue to the underlying muscle. Muscle fascia exposed but not violated.

Grade IV: Ulceration extending through muscle to bone or involving any joint space or supporting structures (such as tendon).

There are two other classification systems, Shea and Yarkony-Kirk, with parameters similar to those of the National Pressure Ulcer Advisory Panel classification. None of these classifications takes into account presence of infection, amount of necrotic tissue, or size of the ulcer.

Wound management is based on awareness of the acute, chronic, local, and systemic factors that resulted in wound formation. The premorbid status, with particular attention to nutritional history and ambulatory status, is critical to management.

The principles of pressure sore management are the following:

- Prevention
  - Education of staff
  - Identification of high-risk patients
  - Precautions
- Early identification of skin impairment
- Debridement
- Treatment of infection
- Local wound care

- Pressure dispersion
- Optimization of global medical status
- Definitive wound closure

Pressure sores are best evaluated by history and physical. Clinical findings can guide the initial management of most pressure sores without costly additional studies. Initial management should focus on the identification of active infection. This is suspected when wound edge cellulitis, purulent discharge, and/or foul odor are present [6]. The gold standard for a diagnosis of osteomyelitis is bone biopsy. More recently, though, magnetic resonance imaging has become a useful noninvasive tool that is very sensitive for the diagnosis of osteomyelitis. The overall clinical condition of the patient should determine the aggressiveness of workup and surgical intervention. Most often, the diagnosis can be made by physical examination, and other studies rarely provide more information. Debridement is probably best limited to infected and obviously necrotic tissue until nutritional status has been optimized.

Most grade I and II pressure sores respond well to debridement, control of infection, and pressure dispersion if the patient is stable medically. Nonetheless, these sores require careful attention despite their initial, relatively innocuous appearance. As discussed previously, the skin is more resistant to pressure than the underlying muscle and subcutaneous fat; this may result in necrotic tissue beneath intact skin. Not infrequently, what may initially appear to be a grade I or II ulcer may actually be a grade III or IV lesion before the eventual loss of the overlying skin.

Ideally, wound debridement will consist of the removal of all necrotic tissue and evacuation of pus and any infected material. This can be performed by sharp debridement or with enzymatic agents with the additional assistance of frequent dressing changes. Extent and aggressiveness of debridement at the authors' institution is often tempered by the clinical status of the wound (infected or noninfected, wet vs. dry necrotic tissue) and the clinical status of the patient (severity of anemia, hemodynamic stability, severity of malnutrition, presence of sepsis). Decisions about wound management are made on a case-by-case basis in conjunction with the ICU and infectious disease teams.

Debridements can commonly be performed at the patient's bedside with appropriate lighting and instruments. Most patients require little or no anesthetic for the debridement of frankly necrotic material. Wound cultures will provide data regarding bacterial colonization. Colonization of pressure sores is polymicrobial. *Bacteroides, Pseudomonas, Proteus, Staphylococcus,* and *Streptococcus* species as well as other enteric flora are the most commonly cultured organisms.

Fortunately, invasive sepsis from a pressure sore is rare. Anecdotally, most cases of sepsis are secondary to abscess formation under an unroofed dry eschar. Sepsis more commonly results from a urinary tract infection or pneumonia. In cases in which the source of sepsis is unclear, computed tomography scanning of the soft tissue or surgical exploration of pressure sores may be mandated. When sepsis is attributed to a pressure sore, the mortality rate is high [22]. Parenteral antibiotics are administered only in the presence of sepsis or if wound closure is planned.

Currently, it is recognized that most topically applied antimicrobial agents and detergents have a toxic effect on human fibroblasts and keratinocytes [15,21–29]. Detergents are used for cleansing the skin surrounding the ulcer. Topical antibiotics such as dilute Dakin's solution or neomycin irrigant help control bacterial colonization in highly contaminated wounds with minimal adverse effect on fibroblasts and keratinocytes [30].

A moist environment with minimal bacterial contamination is desirable for the optimization of reepithelialization. Wet-to-moist dressings with normal saline are recommended as the initial treatment of most grade III and IV pressure ulcers. If the wound is limited to the skin or superficial subcutaneous tissue, an occlusive hydrocolloid dressing may be used as an alternative to wet gauze dressings if the wound has been adequately debrided [31]. Xakellis and Chrischilles [32] performed a prospective randomized study comparing hydrocolloid versus saline gauze dressings in the treatment of pressure ulcers in the long-term care setting. Hydrocolloid treatment required one-eighth the nursing time required by saline gauze treatment. There was no statistically significant difference in the healing time between the study groups; however, the cost was 3.3 times greater in the hydrocolloid group. The value of reducing the time nurses spend on dressing changes may translate into improved overall care of the patient. If an occlusive dressing is applied, fecal contamination under the dressing must be prevented.

Grade III and IV ulcers are treated, in principle, the same as grade I and II ulcers. In the case of exposed or devitalized bone, debridement of all necrotic tissue is necessary. Plain films, bone scans, and erythrocyte sedimentation rates are very nonspecific and generally provide little useful information to support the diagnosis of osteomyelitis. One must rely on clinical suspicion, magnetic resonance imaging, or bone biopsy to confirm the diagnosis. Again, the treatment is focused on adequate debridement, local wound care, pressure dispersion, and nutritional support. Prolonged parenteral antibiotics for bone exposure alone are not recommended unless a definitive debridement and wound closure are contemplated. Some patients may require multiple serial debridements until the wound is controlled.

At the authors' institution, the management of eschars is primarily dictated by the clinical status of the eschar. If the eschar is dry, firm, immobile, and shows no evidence of infection, the eschar is often dressed with silver sulfadiazine twice a day to lower bacterial counts and serially reevaluated until it begins to soften and slough. The necrotic tissue is then debrided at that time. This is done to allow time for healing and allow nonviable tissue to clearly demarcate itself, thereby minimizing the amount of healthy tissue that will be excised at the time of debridement. Eschars that are soft, soupy, mobile, or have evidence of infection are debrided early. On rare occasion, a computed tomography scan may assist in making the decision to observe what may appear to a stable ulcer, when there is a concern of underlying infection that is not apparent on physical examination.

After initial sharp wound debridement, subsequent debridement may be facilitated with the use of topical enzymes. Collagenase ointment facilitates eschar separation and is most applicable in chronic conditions. It works well at removing fibrinous exudate overlying healthy tissue in the base of grade III and IV pressure sores. Enzymatic debridement is particularly useful in patients with intact sensation, in whom surgical debridement at the wound margins may be painful. Collagenase is generally applied once a day with a topical antibiotic powder. Once all eschar is separated and fibrinous exudate removed, the collagenase ointment should be discontinued. Calcium alginate products minimize bacterial contamination and are highly absorbent. They may be useful in treating wounds with a high exudative component after adequate debridement. Enzymatic debridement is a good adjuvant therapy in pressure sores but should not be considered a substitute for sharp debridement. Clinical judgment and experience should dictate its use and application.

An increasingly utilized option in the management of Stage III/IV pressure ulcers is the use of negative pressure wound therapy (NPWT) known as the vacuum-assisted closure (V.A.C.®). This device applies subatmospheric pressure to the wound bed through a secured foam dressing [33]. The V.A.C.® is thought to improve the status of chronic "unsalvageable" wounds in

four ways: decreased time for granulation tissue and wound contracture, reduced bacterial colonization, decreased edema, and minimized dressing changes [33,34].

Several studies have focused on the use of the V.A.C.® for pressure sores. Isago et al. treated 10 patients with Stage IV pressure ulcers for 5 weeks. They demonstrated that after V.A.C.® therapy the wound area and depth was reduced by an average of 55% and 61% respectively [35]. Other studies have compared the V.A.C.® with saline, hydrocolloid, or alginate dressings. Overall, patients with V.A.C.® treatment had evidence of more healthy tissue growth [34,36]. Healthpoint system (HP) products offer enzymatic ointments (Accuzyme, Iodosorb, and Panafil) to manage pressure sores. In an article by Ford et al., the NPWT group versus the HP had a decreased number of polymorphonuclear cells and lymphocytes per high-powered field. This translates to increased rates of wound healing and reduced inflammatory changes [37].

Negative pressure therapy has maximum benefits with large wounds with high exudates, tunneling, or undermining [33]. Prior to use, wounds must be adequately prepared. The end points of treatment with wound V.A.C.® therapy depend on whether a patient is a surgical candidate. In such an instance, the V.A.C.® may be used as an adjunct modality until nutritional status is optimized, appropriate antibiotics are instituted, and comorbidities are stabilized. This may allow progression to the point that wound closure is achieved or a lesser surgical procedure may be performed [33].

Once the wound is determined that it will re-epithelialize, V.A.C.® may be discontinued. Nonetheless, it is imperative to assess the wound frequently and document volume changes. If there is no progress or worsens after 2 to 4 weeks of therapy, then it is reasonable to reassess the appropriateness of VAC therapy [33]. Also, it is paramount that patients adhere to strict off loading regimen, maintain an adequate seal, and tolerate dressing changes all of which may be problems in the ICU setting.

Pressure ulcers are a costly healthcare problem and it is estimated that over 1.6 million wounds develop each year, with a cost of $2.2 to $3.6 billion [33]. There is literature to support early initiation of NPWT which may be associated with reduced length of stay at long-term care facilities leading to overall reduced healthcare costs [38]. Philbeck et al. surmised that there would be approximately $9,000 in savings for pressure sores with NPWT versus saline-soaked gauze over a period of 97 days [39].

Nonetheless, there is a paucity of prospective randomized studies evaluating the cost-effectiveness of the wound V.A.C.® with pressure sores. In the future, we need data that will ascertain the role of NPWT in reducing costs. In addition, we need to determine the role of NPWT as an adjunctive therapy in advanced pressure ulcers management.

Newer technologies such as topical growth factors and cultured skin material are evolving, but their current use is still experimental. When the roles of these treatments are defined, they will not substitute conventional measures of wound care. With appropriate treatment, Conway and Griffith [40] found that 30% to 80% of pressure sores healed without surgical intervention during 3 to 6 months.

OPERATIVE TREATMENT

Patients are considered candidates for surgical closure of pressure sores if they have failed the previously described treatment and are otherwise in reasonably good health. The majority of ICU patients with pressure sores do not meet the general criteria for definitive wound closure during their ICU stay. Chronic malnutrition, poor neurologic status, and noncompliance with postoperative protocol are a few of the relative contraindications to definitive wound closure. The wounds of most ICU patients that do require closure will not be closed for weeks to months after the patients' initial ICU admission. At the time of closure, it is critical that the patient's medical condition is stable and has been restored as close as possible to the premorbid state. The wound must also be well controlled. The lack of enthusiasm of surgeons for primary flap closure is related to the high recurrence rate. Evans and Dufresne [41] reviewed their experience with the surgical therapy of pressure sores and found that 82% recurred at the same site in paraplegic patients. Overall, there was a 91% recurrence rate in the same group. The average time to pressure sore recurrence was 18.2 months and pressure sore recurrence was unaffected by the type of closure that was performed. The authors concluded that the physician and the patient must be willing to accept the inevitability of recurrence at the same or other location. Surgical flap closure is reserved for patients in whom healing has plateaued after maximizing all factors. They must also demonstrate the personal and social support necessary to participate in a comprehensive wound care program.

Prior to surgery, nutritional status is optimized. Bowel preparation is based on the surgeon's preference and is individualized according to the wound and the patient. All nonviable tissue is debrided and bony prominences are reduced. This is frequently a staged procedure to minimize hematoma formation and acute blood loss. The goals of wound closure are to eliminate dead space and to provide wound approximation with minimal tension while the patient is positioned in a normal resting posture. The most common reasons for early failure of flap closure are inadequate debridement, hematoma formation, wound tension, and postoperative positioning. Other reasons for failure are uncontrolled spasm, unaddressed limb contracture, infection, and noncompliance with postoperative protocols.

A myriad of options are available for the flap closure of pressure sores. At the authors' institution, rotation advancement flaps based on the gluteal muscles are preferred for sacral ulcer closure due to the ability to safely readvance the flap if a recurrence should occur. Posterior thigh flaps are preferred for the closure of ischial ulcers, and the traditional tensor fascia lata flap is generally used for trochanteric ulcer closure. Patients with trochanteric ulcers should be evaluated for hip joint stability because they may require a Girdlestone arthroplasty if hip dislocation is contributing to pressure sore formation.

Surgery is usually not necessary for definitive wound closure in ICU patients who were previously ambulating and who in the long term will maintain the ability to ambulate. Even grade III and IV ulcers usually heal with local wound care, good nutritional support, and alleviation of the pressure in ambulators. In the rare instance of a refractory sacral pressure ulcer in an ambulatory patient, use of the gluteus muscle should be tempered to minimize the significant disability caused by the sacrifice of this muscle.

POSTOPERATIVE MANAGEMENT

The critical principles of postoperative management are avoidance of compression of the vascular pedicle, minimization of tension on wound edges, obliteration of dead space, adequate drainage, minimization of shear forces, and pressure dispersion. Air-fluid beds are generally used a minimum of 3 weeks postoperatively. This helps to reduce the likelihood of secondary pressure sores. At the authors' institution, air-fluidized beds are used postoperatively in all patients who undergo flap

TABLE 155.1

SUMMARY OF ADVANCES FOR REDUCING RISK OF PRESSURE SORES

- Early identification of patients at risk using standardized risk assessment tools reduces the incidence of skin breakdown [14,38].
- Pressure-reducing bedding maintains transcutaneous oxygen tension [16,17].
- Hydrocolloid dressing reduces nursing time but increases cost compared with saline dressings for pressure sores [30].
- Negative-pressure wound therapy promotes angiogenesis, new tissue growth, and reduced bacterial growth [31–34].

closure of pressure sores. Jackson-Pratt drains are left in place for a minimum of 2 weeks to facilitate the evacuation of any fluid collections and to obliterate dead space underlying the flap. Parenteral antibiotics are continued for an additional 4 to 6 weeks for all patients diagnosed with osteomyelitis. Bone cultures are sent routinely in all cases in which reduction of bony prominences is performed. Attention to urinary and fecal diversion should be maintained. Recently, at the authors' institution, the V.A.C.® has proved a useful tool postoperatively for edema control, wound drainage, and the obliteration of dead space with good success in place of or as an adjunct to Jackson-Pratt drains. It has been used in selected cases immediately after wound closure and on a few occasions after reexploration for hematoma evacuation.

After flap closure, patients are instructed to remain off the flap surface for a minimum of 5 weeks postoperatively. At 5 weeks, a progressive program of gradual return of weight-bearing tolerance on the operative site is started. The greatest challenge is a life-long commitment to self-care that minimizes the risks of the development of pressure sores in patients with long-standing risk factors.

Advances in reducing risks in pressure sores, based on randomized, controlled trials or meta-analyses of such trials as well as prospective studies, are summarized in Table 155.1.

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CHAPTER 156 ■ MANAGEMENT OF THE OBSTETRICAL PATIENT IN THE INTENSIVE CARE SETTING

JOHN G. GIANOPOULOS AND JONATHAN F. CRITCHLOW

Pregnancy is a common occurrence in everyday life. Yet, many women suffer significant risk and even death from the normal physiologic phenomenon of pregnancy. The United States enjoys one of the lowest maternal mortality levels in the world. However, for every 100,000 live births 10 to 12 women die secondary to medical or obstetric complications of pregnancy. It is not uncommon for the intensive care team to care for pregnant patients with critical conditions. Improvements in obstetric, anesthetic, and intensive care have led to the decline in maternal mortality and the shifting of responsible causes [1,2]. Today there are fewer pregnant patients with septic causes for their critical illness and more patients with hypertension and concurrent medical illness admitted to the intensive care setting [3].

The approach to the pregnant patient in the intensive care setting requires a thorough knowledge of the normal maternal adaptations to pregnancy, the potential fetal effects of any diagnostic or therapeutic modalities needed, and the potential for obstetric complication of any procedures. This chapter reviews the maternal anatomic and physiologic adaptations to pregnancy, considerations of potential harm from diagnostic studies, selected therapeutic interventions, and specific pregnancy disease states that may complicate the care of the critically ill pregnant patient such as preeclampsia, eclampsia, obstetric hemorrhage, and trauma. Specifics related to the diagnosis and treatment of respiratory failure in pregnancy is discussed elsewhere in the text (see Chapter 51).

MATERNAL PHYSIOLOGIC ADAPTATION TO PREGNANCY

Cardiovascular System

The cardiovascular system undergoes significant alteration under the influence of the altered hormonal milieu of pregnancy. Cardiac output begins to rise in the first trimester and continues a steady rise peaking at 30% to 50% of preexisting levels by 32 weeks' gestation [4]. The rise in cardiac output is produced by increases in both heart rate and stroke volume which are in response to an increase in endogenous circulating catecholamines, which affect both an inotropic and a chronotropic response [5,6]. Peripheral vascular resistance is reduced secondary to a direct effect of progesterone relaxing the smooth muscle intima of the precapillary resistance vessels, resulting in vasodilatation [6]. The arterial–venous shunt of the placenta also contributes to decreased vascular resistance. In the third trimester, the enlarged uterus may compress the vena cava (particularly in the supine position) leading to decreased venous return to the heart and a decrease in cardiac output. The third-trimester pregnant patient is best positioned so that the uterus is displaced to the left, allowing adequate venal caval flow and venous return to avoid hypotension. There is a slight drop in mean arterial pressure in normal pregnancy beginning during the second trimester secondary to the reduction in peripheral resistance. Blood volume increases in pregnancy, peaking at 50% above prepregnancy levels. The maximal increase in blood volume occurs at about 32 weeks' gestation [7,8]. This increased blood volume leads to normalization of mean arterial pressures by term.

The pulmonic and systemic circulations undergo similar alterations. There is vasodilatation with an increased volume to capacitance. However, in the pulmonic circulation the volume and capacitance changes almost equal each other. Therefore, there is virtually no change in mean pulmonic pressures [9,10]. When the pulmonic circulation is evaluated by central catheterization, no changes in pulmonary artery pressures or wedge pressures can be attributed to pregnancy [9,11]. The increased pulmonic volume with increased capacitance renders the pregnant patient susceptible to fluid overload and pulmonary edema. Pulmonary edema will occur much more readily in pregnancy secondary to these specific maternal adaptations.

Respiratory Adaptations

Progesterone affects the hypothalamic apneustic center. Carbon dioxide sensitivity is reduced to 30 mm Hg. This results in an increased respiratory rate and an increased tidal volume. The pregnant patient is in a chronic state of respiratory alkalosis. The kidneys compensate by excreting bicarbonate to maintain normal acid–base equilibrium [12]. The normal blood gas of pregnancy is a compensated respiratory alkalosis. The normal pH is 7.44 and the bicarbonate decreases 4 mEq per L [12]. Vital capacity and maximum voluntary ventilation are not altered. The functional residual capacity is reduced as the diaphragm is elevated. The reduced bicarbonate level renders the pregnant patient much more susceptible to the development of metabolic acidosis in response to a variety of conditions [12,13].

Hematologic Adaptations

Plasma volume in pregnancy increases by 50% for prepregnancy levels. The red cell mass will increase in pregnancy by 30% over prepregnancy levels. This leads to a dilutional effect, decreasing hemoglobin concentrations (lower normal: 10.5 to 11 g per dL) and hematocrit levels (30% to 35%). This phenomenon has been termed the *physiologic anemia* of pregnancy [8,14].

Increased catecholamine and steroid levels in pregnancy cause a demargination of mature leukocytes from the

endothelium. This leads to a physiologic leukocytosis of pregnancy, with the white blood cell count increasing by 5,000 to 10,000 cells per mL [8,14].

Estrogen stimulates the hepatocyte endoplasmic reticulum, leading to an increased protein production. There is also increased synthesis of several clotting factors (VII, VIII, IX, and X) throughout pregnancy. Fibrinogen increases by 20%, with an average level during gestation of 400 mg. These increases render the pregnant woman hypercoagulable [15]. Critically ill pregnant patients rendered immobile require some form of prophylaxis to prevent venous thromboembolic events as they are at higher risk secondary to the hypercoagulability of pregnancy.

Renal Adaptations

Renal plasma blood flow and glomerular filtration rate increase by approximately 30% to 50% from prepregnant levels resulting in an increased creatinine, urea, and uric acid clearance, with a decrease in serum creatinine (normal: 0.5 to 0.9 mg per dL), blood urea nitrogen (normal: 10 to 15 mg per dL), and uric acid (normal: 2.5 to 3.5 mEq per L) levels [15–17]. When drugs with renal clearance are used in pregnancy, their dose needs to be adjusted to account for increased renal clearance. Progesterone relaxes the renal collecting system. The muscularis of the bladder is relaxed and urinary stasis occurs. The angle of the urethra to the vagina is altered, making urinary tract infections common in pregnancy. If bladder catheterization is required for more than 12 hours, antibiotic prophylaxis is needed to prevent urinary tract infection (Table 156.1).

TABLE 156.1

PHYSIOLOGIC MATERNAL ADAPTATION TO PREGNANCY

System	Alternations
Cardiovascular	Cardiac output, HR × SV = CO Increased 20%–30% Both heart rate and stroke volume increased
Peripheral vascular resistance	Decreased as resistance vessels with vasodilatation
Blood flow	Increased to Uterus Skin Kidney Breast
Pulmonic circulation	Blood volume increases equal capacitance increase No change in pulmonary artery pressures
Pulmonary system	Tidal volume increased Respiratory rate increased Functional residual capacity reduced Compensated respiratory alkalosis
Renal system	Renal artery perfusion increased Glomerular filtration rate increased Creatinine clearance increased BUN, serum creatinine, serum uric acid decreased Renal clearance of drugs increased Bladder muscularis relaxation Urinary stasis infection risk Dilated renal pelvises and ureters
Gastrointestinal system	Decreased gastric motility Aspiration risk with anesthesia Decreased colonic motility Constipation complaints
Hematologic system	Plasma volume increases 40%–50% Red cell mass increases 20%–30% "Physiologic anemia" Leukocytosis Increased liver-produced clotting factors Increased fibrinogen Hypercoagulable state

BUN, blood urea nitrogen; CO, cardiac output; HR, heart rate; SV, stroke volume.
From Gianopoulos JG: Establishing the criteria for anesthesia and other precautions for surgery during pregnancy. *Surg Clin North Am* 75:33, 1995, with permission.

DIAGNOSTIC RADIATION EXPOSURE

Diagnostic radiographic procedures are essential in the management of the critically ill patient. These procedures may be undertaken with care in the pregnant patient. Adverse fetal effects are reported with ionizing radiation exposure to the fetus in excess of 10 cGy [18–20]. Microcephaly, intrauterine growth restriction, and poor fetal development have all been reported [18–20]. Direct radiation exposure to the pelvis of 10 cGy or greater in the first trimester may result in intrauterine fetal death. Direct fetal exposure of 5 cGy or less has not been shown to increase fetal malformation. However, a very small risk of increased childhood malignancy has been reported. Direct doses of 1 cGy or less have not been shown to produce any significant fetal effect [18–20]. Single-shot examinations such as chest radiographs, abdominal images, or imaging of long bones expose the fetus to very little risk. Fluoroscopic examinations are to be avoided in pregnancy because of the significant amount of radiation exposure [19,20].

Computed tomography (CT) of the head and thorax produces little direct radiation to the pelvis (0.05 to 0.1 cGy) and may be undertaken with relative safety [21]. Abdominal and pelvic CT scanning delivers 3 to 10 cGy to the pelvis and should be avoided in the first trimester. In the second and third trimester, abdominal and pelvic CT examinations may be done with caution [21,22]. If a significant alteration in management is to be undertaken as a result of the information obtained from the procedure, the potential fetal risk should be considered. Magnetic resonance scanning has not been extensively studied in pregnancy. However, this technology is considered extremely safe in pregnancy and may be an alternative to CT scanning in the first trimester [23,24]. Magnetic resonance imaging examinations are used as an adjunct to ultrasound in the second and third trimesters to aid in the diagnosis of certain fetal anomalies. Contrast agents should be avoided in the first trimester [23,24].

Radionuclide procedures may be done in pregnancy. The overall radiation dose to fetus with most procedures is low. Most of the contrast agents used in these examinations are renally cleared. It is important to place an indwelling bladder catheter to reduce total radiation dose to the fetus because retained urine in the maternal bladder could expose the fetus to larger radiation doses than the initial pass through the placental circulation [19,25–27].

TABLE 156.2

RADIATION DOSE AND FETAL EFFECT

Radiation dose to fetus (cGy)	Theoretical or actual fetal effect
0–5	No reported malformation; potential for oncogenesis and increased cancer risk
5–10	Potential for oncogenesis; potential for IUGR
10–20	Microcephaly, IUGR, 2.4% mental retardation
20–50	Microcephaly, IUGR, fetal death, mental retardation
50–100	Microcephaly, IUGR, 18% mental retardation, fetal death

IUGR, intrauterine growth retardation.
From Gianopoulos JG: Breast disease in pregnancy, in Isaccs JH (ed): *Textbook of Breast Disease*. Philadelphia, Mosby-Year Book, 1992, p 131, with permission.

If excessive radiation doses to the pelvis are inadvertently administered, it is important to calculate the fetal isodose radiation exposure. If an excess of 10 cGy has been delivered to the fetus, there may be significant fetal effect. Table 156.2 outlines potential fetal effects of radiation exposure.

MEDICATIONS AND PREGNANCY

Analgesic Agents

Opiate narcotic agents administered for short periods of time have been shown to be safe in pregnancy. Morphine and meperidine administered intravenously, intramuscularly, or in patient-controlled pumps, have demonstrated no adverse fetal effects. Chronic opiate use in pregnancy has been associated with intrauterine growth restriction. Intrauterine fetal addiction with withdrawal may occur [28–30]. Intrauterine fetal withdrawal has been associated with intrauterine fetal demise. Oral opiates may be used with similar cautions.

Codeine-containing compounds should be avoided in the first trimester because they have a small teratogenic potential [30]. These compounds may be used in the second and third trimesters for short intervals with little fetal risk. Nonsteroidal anti-inflammatory agents may decrease fetal renal blood flow, leading to oligohydramnios. They also will lead to the in utero closure of the ductus arteriosus, producing fetal pulmonary hypertension after 32 weeks' gestation. Short courses of indomethacin may be used with caution prior to 32 weeks' gestation. Benzodiazepines may be used; they have not been shown to exert an adverse fetal effect. High doses near the time of delivery may lead to neonatal depression [30,31].

Antibiotics

Penicillin, penicillin derivatives, as well as cephalosporins have no known adverse fetal effect. Erythromycin, clindamycin, and vancomycin are considered safe in pregnancy. There is some concern regarding renal toxicity with vancomycin. Aminoglycosides have been implicated with fetal ototoxicity [30]. However, only streptomycin and kanamycin have been implicated. Gentamicin has not been reported to have significant ototoxicity. Gentamicin may be used in life-threatening infections while carefully monitoring levels. Sulfonamides complete with bilirubin-binding sites and may lead to neonatal kernicterus if administered in the third trimester. Tetracycline is teratogenic, leading to brown teeth and abnormal long bone development [30,32,33] (Table 156.3).

TABLE 156.3

ANTIBIOTICS IN PREGNANCY

Penicillin/cephalosporin
- No adverse effect in nonallergic patient

Aminoglycosides
- Renal toxicity and ototoxicity
- Use in life-threatening infections

Tetracycline
- Contraindicated
- Staining of teeth
- Bone demineralization

Sulfa drugs
- Avoid first trimester
- Third trimester use with bilirubin displacement
- Kernicterus

Chloramphenicol
- Grey baby syndrome

Fluoroquinolones
- Fetal effect—avoid use

From Gianopoulos JG: Establishing the criteria for anesthesia and other precautions for surgery during pregnancy. *Surg Clin North Am* 75:33, 1995, with permission.

Anticoagulants

Unfractionated heparin, because of its molecular size and ionic negative charge, has been shown not to cross the placental membrane [34]. Therefore, it is the anticoagulant of choice in all trimesters of pregnancy and may be used with relative fetal safety. Fractionated heparins also have been shown not to cross the placental membrane. They may be used throughout pregnancy as well. If fractionated heparins are used in pregnancy, it is advised to change to unfractionated heparin late in the third trimester. If surgical intervention is needed, unfractionated heparin may be reversed with protamine sulfate and the activated partial thromboplastic time is a more reliable monitor for anticoagulant effect than the activated factor Xa assessment needed to assess the activity of fractionated heparins [35,36]. Warfarin and its derivatives are contraindicated in the first trimester as these agents are teratogenic, producing midline defects such as clefts, cardiac septal defect, and limb bud abnormalities. In all trimesters, warfarin crosses the placenta and may lead to spontaneous fetal bleeding [37–39]. In some select cardiac patients (particularly those with mechanical valves), warfarin may be used in the second and early third trimesters. Fetal intracranial bleeding has been observed with warfarin use in the late third trimester.

Antihypertensives

Pregnant patients will require acute antihypertensive intervention when the systolic blood pressure exceeds 160 mm Hg or the diastolic blood pressure exceeds 110 mm Hg. Preservation of the fetal circulation must be kept in mind when treating these conditions. For the acute management of hypertensive crisis in pregnancy, hydralazine has been recommended [40,41]. A test

dose of 5 mg intravenous (IV) is given, followed by 10-mg doses. However, recent data show labetalol may be a superior antihypertensive in acute situations, as it does not increase the maternal pulse rate. A 10-mg test dose is given IV, followed by a 20-mg dose at 10 minutes if no response is observed. If still no response in blood pressure is observed, the dose may be increased to 40 mg in 10 minutes and followed by 80 mg in 10 minutes. The 80 mg dose may be repeated one time. The total dose should not exceed 220 mg. Labetalol may also be administered as a continuous IV drip at 2 to 4 mg per minute [42,43]. Nifedipine may be used in less acute conditions with caution due to paradoxical hypotension. Hydrating the patient with IV fluids will reduce the incidence of a decrease in blood pressure

Sodium nitroprusside should be avoided if possible. This agent is converted in the fetus to sodium thiocyanate, which cannot be metabolized because the fetus lacks the necessary hepatic cytochrome. In extreme situations when other agents have not been effective, it may be used with caution [44–46]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blocker agents are contraindicated in pregnancy. They have been associated with fetal anomalies and intrauterine fetal death secondary to fetal cardiovascular collapse [30].

Vasoconstrictor and Inotropic Agents

Profound hypotension unresponsive to postural change and fluid resuscitation may require vasoconstrictor therapy. Phenylephrine has been shown to be safe in treating hypotension secondary to spinal or epidural anesthesia. Its excessive alpha activity makes it less effective in treating critically ill patients. Dopamine and isoproterenol alter uterine blood flow less than phenylephrine. In situations in which vasoconstrictor therapy is needed in a critically ill patient, dopamine is recommended. At low doses, 2 to 4 µg per minute, uterine blood flow is increased [46,47].

SPECIFIC PREGNANCY DISORDERS

Hypertensive Disorders of Pregnancy

Hypertension complicates 8% to 10% of all pregnancies, yet despite modern medical management it continues to be a leading cause of maternal mortality. Hypertension during pregnancy is classified as preexisting chronic hypertension, preeclampsia/eclampsia, chronic hypertension with superimposed preeclampsia, and gestational hypertension [42].

Preeclampsia is defined as proteinuric hypertension after the 20th week of gestation. Hypertension is defined as a sustained blood pressure of 140 mm Hg systolic and/or 90 mm Hg diastolic. Proteinuria must exceed 300 mg in 24 hours. A dipped urine sample of 1+ repeated in 6 hours or a single 3+ or 4+ dip also will meet the criteria to make the diagnosis. Preeclampsia may lead to significant maternal end organ damage, secondary to vasospasm [42,48]. The organ dysfunction leads to with renal failure, liver compromise, intravascular coagulopathy, thrombocytopenia, pulmonary edema, hemolysis, and cardiac failure. Preeclampsia is classified as mild or severe. Severe preeclampsia occurs when any of the following criteria are met: blood pressure 160/110 mm Hg, thrombocytopenia, elevated liver enzymes, oliguria, proteinuria in excess of 5 g in 24 hours, hyperreflexia, scotomata, epigastric pain, renal failure, pulmonary edema, disseminated intravascular coagulopathy, and fetal compromise. Mild preeclampsia is preeclampsia without any criteria met to classify as severe. Eclampsia is defined as preeclampsia with the onset of maternal seizure in a patient without previous seizure disorder.

The specific etiology of pre-eclampsia remains a medical enigma. However, much is known regarding the underlying pathophysiology of this disease. Arteriolar vasospasm with intravascular volume depletion is the primary pathologic alteration leading to preeclampsia. Precipitating pathologic factors include failure of prostacyclin-mediated vasodilatation in the vascular system, endothelial damage leading to the release of endothelins, thromboxane, and vasoactive proteins [49–51]. Placental vascular growth factor inhibitory proteins have been implicated in the etiology.

These intravascular changes lead to the loss of catecholamine insensitivity of normal pregnancy and angiotensin hypersensitivity. The increase in peripheral vascular resistance leads to hypertension, diminished blood flows to vital organs, and microangiopathy. Albumin concentrations decrease in the blood secondary to proteinuria which contributes to a decrease in plasma oncotic pressure. This, along with endothelial damage, leads to generalized edema, ascites, and in severe cases, pulmonary edema. Renal blood flow is decreased and fibrin deposition occurs in the glomeruli. Renal endothelial cells swell and the filtration function of the kidney is impaired, allowing large protein molecules to enter the collecting tubules [52]. Hyperreflexia is common. The mechanism responsible for central nervous system dysfunction is not totally understood. Hypertensive encephalopathy, cerebral vasospasm, and cerebral edema contribute to the pathologic milieu, which may lead to an area of localized cerebral irritability leading to an epileptic focus resulting in seizure activity.

A syndrome of hemolysis, elevated liver enzymes, and low platelets is sometimes seen in patients suffering from preeclampsia and is termed the HELLP syndrome [53]. This constellation of end organ abnormalities may be seen in 2% to 12% of patients with preeclampsia. As many as 30% to 50% of these patients may not manifest hypertension or proteinuria. This syndrome is a severe form of preeclampsia and is life threatening. The exact pathogenesis is not known; however, vasospasm, endothelial damage, and microangiopathic hemolysis all contribute. Platelet consumption and fibrin deposition in the liver lead to areas of necrosis. Rarely, subcapsular hematoma may occur. The diagnosis is made by the observation of hemolysis on peripheral blood smear, elevations in lactate dehydrogenase, alanine aminotransferase, and thrombocytopenia (platelet count less than 100,000 per mm^3) [53]. Occasionally, in very preterm gestations, one may treat this condition conservatively with IV steroids (dexamethasone, 10 mg IV every 6 hours). However, a randomized trial assessing this therapy failed to show any improvement in most cases. There was a minimal effect in the most severe cases however. This therapy may be used with very preterm infants [54,55]. In most cases, especially in the mid-to-late third trimester, delivery is warranted [42].

Management

The definitive treatment of preeclampsia is delivery. At term, patients should be stabilized and delivery effected. A preterm pregnancy may be treated conservatively if no signs of severe preeclampsia are observed [42,48]. In select cases of severe preeclampsia, remote from term patients may be followed in a tertiary care setting conservatively. The agents of choice for the treatment of hypertension are hydralazine or labetalol. Labetalol acts on both alpha- and beta-receptors without increasing the heart rate [54]. Patients remote from term should be given steroids to enhance fetal pulmonary maturity (betamethasone, 12 mg intramuscularly [IM] every 24 hours for two doses or dexamethasone, 6 mg IM every 12 hours for four doses). Tests of fetal well-being with ultrasound and fetal monitoring

(nonstress test) should be performed. In severe cases (particularly with oliguria or pulmonary edema), invasive maternal hemodynamic monitoring may be beneficial. Diuretics should not be used unless pulmonary edema is present, as intravascular volume is already depleted. At the time of labor or in severe cases, IV magnesium sulfate is the analeptic of choice. It has been shown to be superior to other agents in randomized trials at preventing eclamptic seizures [56–59]. A loading dose of 2 to 4 g is given IV slowly during 15 to 20 minutes. This is then followed by a maintenance dose of 1 to 2 g per hour. Magnesium levels may become toxic, leading to respiratory or cardiac arrest [56,57]. These patients require intensive monitoring of their respiratory function, cardiovascular function, and neurologic status. As magnesium is renally cleared, adequate urine output must be maintained. If patients manifest oliguria, a decrease or discontinuation of magnesium is indicated. Magnesium toxicity may be reversed with the administration of IV calcium (10 mL of a 10% solution of calcium gluconate given slowly IV over 10 minutes).

Eclamptic seizures are treated with IV magnesium. In cases unresponsive to magnesium, benzodiazepines may be used, such as diazepam (5 to 10 mg IV). When the seizure activity persists, the next agent of choice is phenytoin (10 to 20 mg per kg IV during 20 minutes). If the seizure still continues, IV amobarbital in 50-mg increments to a total dose of 200 mg is administered. In severe refractory cases, muscle paralysis with general anesthesia and ventilatory support is needed [57,59,60].

Patients with severe disease during weeks 24 to 28 of pregnancy are treated conservatively with aggressive maternal support and steroids for fetal lung development. An attempt should be made to achieve a gestational age of 28 weeks, if the maternal and fetal condition remains stable. From 28 to 34 weeks, steroids are given and delivery should be undertaken within 48 hours, if the maternal and fetal conditions remain stable. When severe pre-eclampsia presents after 34 weeks of gestation, delivery should occur after maternal stabilization [59]. The route of delivery should be determined by obstetric factors and vaginal delivery may be undertaken.

Rarely, patients may rupture a subcapsular liver hematoma. This manifests with severe right upper quadrant and shoulder pain. If shock ensues, immediate operation is needed. In more stable patients, the diagnosis may be confirmed with ultrasound or CT scan.

Obstetric Hemorrhage

Despite medical interventions, obstetric hemorrhage remains a significant cause of maternal morbidity, mortality, and fetal loss. Physiologic changes in the uterine blood flow increase uterine artery blood flow to 500 to 600 mL per minute at term. Patients in the third trimester with placental disruptions such as placenta previa or abruption may suffer rapid and significant blood loss, leading to hemodynamic compromise. Hemorrhage in the third trimester of pregnancy is an acute medical emergency.

There is a normal physiologic blood loss at the time of delivery. In an average vaginal delivery, the patient may lose 300 to 500 mL, and this increases to 1,000 to 1,500 mL with cesarean section [14]. When significant hemorrhage occurs, prompt medical or surgical intervention is needed.

Antepartum Hemorrhage

First and second trimester conditions such as spontaneous abortion and ectopic pregnancy may lead to significant blood loss. Patients treated for spontaneous abortion or ruptured ectopic gestation need continuous hemodynamic monitoring and aggressive fluid and blood product replacement to avoid hemodynamic compromise and hypovolumic shock. Third trimester bleeding is most often placental in nature, such as abnormal placental location, placenta previa or premature placental separation from the uterine wall (abruption placenta).

Placenta Previa

The placenta is located over the cervical os in 1 in 150 to 200 pregnancies. These patients usually present with painless vaginal bleeding and may have multiple sporadic episodes of bleeding. The diagnosis is made ultrasonically with observation of the placenta covering all or part of the cervical os [60,61]. The bleeding episodes are usually self-limiting, although sometimes the bleeding will not remit and immediate cesarean section is warranted. Once the diagnosis is made, these patients are treated with conservative management. Bed rest, blood replacement, and close surveillance of maternal and fetal well-being are the mainstays of therapy [61]. In stable cases remote from term, patients with good family support at home, may be treated as outpatients. Most cases near term require hospitalization and close monitoring. If stable, patients are assessed for fetal lung maturity with an amniocentesis at 35 to 36 weeks and cesarean section is preformed if fetal lung maturity is documented [61]. Rarely, the placenta may invade the myometrium (accreta abutting the myometrium, increta invading partially into the myometrium, and percreta invading through the myometrium). These conditions often will require hysterectomy at the time of cesarean operation. These procedures incur significant blood loss and these patients need close postoperative monitoring for hemodynamic status [61].

Abruption Placenta

Placental abruption, the premature separation of the placenta from the uterine wall, complicates up to 1% of all pregnancies. This condition may lead to severe vaginal bleeding or may be concealed within the uterus. These patients have a significant risk of coagulopathy, and coagulation studies are indicated. The therapy consists of maternal stabilization with fluid and blood product replacement, if necessary, and fetal monitoring since fetal mortality rates may be as high as 25% to 40%. Fetal loss is more likely if fetal maternal hemorrhage has occurred, and assessment of fetal blood in the maternal circulation with Kleihauer–Betke testing is indicated. If coagulopathy ensues (as is seen in 15% to 30% of these cases), resuscitation with blood-replacement products such as fresh-frozen plasma or cryoprecipitate is necessary [62]. At term, delivery is indicated. With preterm presentation, if the abruption is not severe and maternal and fetal status are stable, an attempt at conservative management with intensive surveillance may be undertaken. In these cases, steroids are given to enhance fetal lung maturity. At the time of delivery, bleeding may be vigorous and operative interventions such as uterine artery ligation, hypogastric artery ligation, radiographic directed embolization, or hysterectomy may be necessary [62].

Postpartum Hemorrhage

Significant hemorrhage postpartum occurs in 2% to 5% of deliveries. The most common cause is uterine atony in the immediate postpartum period. Retained placental fragments, lacerations of the cervix and vagina, and unrecognized coagulopathies are other potential causes [63]. Blood loss of more than 500 mL at vaginal delivery or 1,000 mL at cesarean section is classified as postpartum hemorrhage [16]. Delayed hemorrhage, 3 to 7 days postpartum, most often is due to retained

placental fragments or unrecognized congenital coagulopathies [63].

The immediate management consists of an investigation for the cause. Careful examination of the cervix and vagina to assess for unrecognized lacerations is warranted. Assessment of the contractile status of the uterus is also performed. In cases of atony, uterine oxytocic agents are administered. Oxytocin solutions are given IV (20 to 40 units added to 1 liter IV solutions and administered at 200 to 300 mL per hour) [63–65]. Vigorous external uterine massage is also used. In most cases, this is all that is necessary to resolve the problem. If atony persists, ergot-containing agents such as Methergine, 0.2 mg IM, may be used. These compounds are contraindicated in patients with hypertension as significant elevations in blood pressure may occur and rarely may lead to intracerebral hemorrhage. Prostaglandin agents of the F2 alpha class (Hemabate, 250 µg) may be given intramuscularly [65,66]. These agents may cause significant bronchospasm and are contraindicated in patients with asthma. Assessment for coagulopathy is warranted in unresponsive cases [66,67].

If medical management is unsuccessful, surgical intervention is needed. An intrauterine examination under anesthesia for retained products and dilatation and uterine curettage may be performed. If still unresponsive, angiographic uterine artery embolization or surgical intervention with uterine artery or hypogastric artery ligation is needed. In cases of unresponsive atony, uterine-constricting suture of the B Lynch type may be employed. If all measures have failed to resolve the bleeding, hysterectomy may be employed as a last resort [68,69].

Amniotic Fluid Embolism

Amniotic fluid embolism presents as a sudden and acute cardiovascular and respiratory collapse at or around the time of delivery. In the past, this condition had an 80% to 100% maternal mortality. Most cases follow vaginal births, but cases have been associated with abruption, ruptured uterus, and second and early third trimester abortions. Today, with rapid identification and maternal cardiovascular and respiratory support, the mortality rate has been reduced to 50% [70,71]. Amniotic fluid contains many vasoactive and fibrinolytic compounds that, if extravasated into the vascular space, may cause an immediate cardiovascular collapse, with respiratory failure. Immediate and aggressive intervention is necessary to save the mother's life. Intubation and mechanical ventilation with positive end-expiratory pressure is employed. Inotropic and vasoconstrictor agents are needed for cardiac and vascular support. Invasive right-sided cardiac monitoring is also indicated. Blood from the pulmonary artery should be assessed for fetal squamous cells. If found, the diagnosis is confirmed, although the absence of these cells does not preclude the diagnosis [72]. These patients will often experience a rapid and fulminant disseminated intravascular coagulation, requiring resuscitation with fresh-frozen plasma and cryoprecipitate. These patients require intensive monitoring and support (see Chapter 51). If the patient survives the initial insult, most will survive [72–74].

Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura

Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura rarely occurs in pregnancy. It is often confused with preeclampsia. Renal failure, thrombocytopenia, and hemolysis are observed in the hemolytic uremic syndrome. If neurologic symptoms are observed, thrombotic thrombocytopenic purpura is diagnosed. This rare condition carries a high maternal mortality if not recognized and rapidly treated. It occurs late in the third trimester or in the immediate postpartum period [75]. Thrombotic occlusion of the microvasculature with platelets leads to hemolysis, producing the findings of this syndrome [75,76,77]. Plasma exchange should be initiated immediately, as it is the most effective treatment for this condition. In some patients as an adjunct to plasma exchange, high-dose IV steroids have sometimes been used with some positive effect on outcome. Patients will usually recover if aggressive therapy and support through their renal failure phase is undertaken early in the course of the disease [77–79].

Burn Injuries

Pregnancy does not alter the acute management of the patient suffering from burn injuries. Aggressive fluid replacement therapy, antibiotics, and oxygen therapy are the mainstays of treatment. The fetal outcome is related to the severity of the maternal burn injury and the development of any maternal complications [80]. If maternal burn injury exceeds 50%, the fetal mortality approaches 100%. In the third trimester, if maternal burn injury is greater than 50%, delivery is indicated. If the maternal burn is 30% or less, fetal survival approaches 80% [80]. Fetal death usually occurs in the first week flowing the burn injury. If the fetus is remote from term, steroids for fetal lung maturity are indicated. If preterm labor ensues and the maternal burn injury is less than 30%, uterine-relaxant tocolytic agents are indicated. Septic complications of burn wound and frank maternal sepsis may lead to labor or fetal amnionitis. Broad-spectrum antibiotics, tetanus toxoid, and immunoglobulin therapy are not contraindicated in pregnancy. Prompt and aggressive therapy for the maternal burn injury produces the best pregnancy outcomes [81].

Trauma Complicating Pregnancy

Trauma is the most common cause of death in pregnancy not related to obstetric factors. Six percent to 7% of pregnant patients will suffer a traumatic injury during their pregnancy. However, less than 1% will require hospitalization [82].

The physiologic alterations of pregnancy, particularly the increased blood volume, make the pregnant trauma patient less likely to immediately manifest signs of shock, although uterine blood flow may be compromised early and fetal compromise is common. The abdominal position of the uterus in the third trimester makes this organ more susceptible to both blunt and penetrating trauma. As the uterus grows, the bladder is pulled superior and rendered more susceptible to traumatic injury in pregnancy.

Motor vehicle accidents with either deceleration forces or blunt trauma are the most common mechanisms occurring during pregnancy. They account for 60% of injuries in pregnancy. The pregnancy outcome is directly related to the severity of the maternal injuries. The most common cause of fetal death is maternal death [83,84].

Following blunt injury secondary to a motor vehicle accident, placental abruption is the most common complication associated with the pregnancy. Abruptions occur in 2% to 4% of patients with these injuries. Ultrasound to detect abruptions is not sensitive, having only 20% to 30% sensitivity [84–86]. Fetal contraction monitoring is a sensitive measure for the diagnosis of abruptions. Contraction monitoring has a high negative predictive value. Most abruptions will occur in the first 4 to 8 hours postinjury. No consensus exists as to the length of the post-trauma monitoring interval, but at least 4 hours is recommended [87,88]. Rarely, a delayed abruption up to 48 hours postinjury may occur. There is no sensitive test to predict

delayed abruption. However, if fetal maternal hemorrhage is observed, the incidence is higher. All patients should be screened with a Kleihauer–Betke assay to assess for fetal–maternal bleeding [89]. If positive, a longer period of observation is warranted. As small amounts of fetal blood may enter the maternal circulation, all patients require blood typing and assessment of Rh status. All Rh-negative patients should receive prophylaxis with Rh immunoglobulin, 300 µg, to prevent isoimmunization. The mother and fetus require continuous monitoring. The usual markers of severity of maternal illness—blood pressure, heart rate, hematocrit, and arterial partial pressure of carbon dioxide—are not predictive of fetal outcome. All maternal injuries need to be treated as they normally would be, regardless of the pregnancy. Pneumatic antishock devices should be avoided in the pregnant patient, as uterine blood flow is dramatically decreased by these devices. Imaging studies with ultrasound are the first line for assessment. In the second and third trimesters, CT scans of the abdomen and pelvis may be undertaken but they expose the fetus to 5 to 7 cGy of radiation. If peritoneal lavage is necessary, it may be performed with care taken to avoid the uterus during catheter insertion; either an open technique or using ultrasonic guidance are preferable. In severe cases, cesarean section may improve maternal outcome, by removing the placental arteriovenous shunt [90].

Penetrating Trauma

Penetrating injuries to pregnant patients most commonly are gunshot wounds or knife wounds. Pregnant patients have a better prognosis after penetrating abdominal trauma as the large muscular uterus protects maternal vital organs. Maternal visceral injuries complicate 19% of penetrating abdominal trauma with a 3.9% maternal mortality rate [91]. The anterior and central location of the uterus subjects the fetus to significant risk with penetrating wounds. The fetus is injured in 66% of these cases, with a high 40% to 70% fetal mortality rate [92]. The management of these injuries remains controversial. Many experts advocate surgical exploration. Conservative management with imagining and observation also may be considered. Lower abdominal penetrating injuries have a less likely chance of producing maternal organ injury, but carry a significant risk of fetal injury. The best management is to individualize assessment with aggressive surgical intervention when fetal or maternal indicators warrant. A coordinated effort between the trauma surgeon and obstetrician will provide the best outcome for both mother and fetus [91–93].

Advances in management of critically ill pregnant patients, based on randomized controlled trials or meta-analyses of such trials, are summarized in Table 156.4.

TABLE 156.4

SUMMARY OF ADVANCES IN MANAGEMENT OF THE CRITICALLY ILL PREGNANT PATIENT AS IDENTIFIED IN RANDOMIZED CONTROL TRIAL DATA

- Magnetic resonance imaging is used in the second and third trimesters to aid with fetal diagnosis [25,26].
- Magnesium sulfate is preferred treatment for preeclamptic seizures at the time of labor [57,59].
- Coagulopathy associated with abruption placenta should be managed with replacement blood products [64].
- Dexamethasone to treat HELLP syndrome only has minimal affect in the most severe cases [55].

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ARTHUR L. TRASK · STEPHEN L. BARNES

CHAPTER 157 ■ SHOCK: AN OVERVIEW

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Shock is one of the most complex conditions encountered in the critically ill patient. The term "shock" encompasses a broad range of pathologic processes that may require diametrically opposed methods of treatment. The underlying cause may be quite evident, as in traumatic hemorrhage, or occult, as in severe sepsis due to infection. Delayed shock resuscitation is associated with significant morbidity and mortality. Therapy must commonly be initiated before all clinical information and diagnostic studies are available. As a result, the intensivist must possess a solid understanding of the common shock states, their clinical presentation, and the necessary therapeutic interventions. Although mortality remains high, increasing application of early goal-directed resuscitation to achieve defined physiologic endpoints has significantly improved patient outcome from shock [1–3].

Over the centuries, shock has been defined in various ways. In 1534, Ambrose Pare wrote that shock was caused by "toxins in the blood" and recommended phlebotomy as the treatment, a practice that persisted until the early 1800s. By that time, shock-associated hypotension was well recognized as was the detrimental impact of bloodletting on systemic perfusion [4]. Although subsequent early definitions of shock lack scientific terminology, they compensate for this in their simplicity. John Collins Warren described shock as "a momentary pause in the act of death," whereas Samuel David Gross defined shock as "a rude unhinging of the machinery of life" [5]. In the 1930s, Alfred Blalock published his classic series of investigations into shock confirming that hypotension was due to loss of blood and plasma into the tissues (so called "third-space losses" due to increased capillary permeability) [6]. Blalock found that the hypotension and high mortality of shock were reversible through the infusion of crystalloid solutions to replace lost intravascular and interstitial fluid, and that simple reinfusion of lost blood was not sufficient. Shock was thus identified as a systemic disorder caused by increased vascular permeability, interstitial edema, and intravascular volume depletion with the classic signs of hypotension, decreased urinary output, and multiple organ failure.

The importance of regional end-organ perfusion, rather than simply systemic blood flow alone, is the singular concept for recognizing and improving patient outcome from shock. Perfusion may be decreased either systemically (as in hemorrhagic or cardiogenic shock) or only regionally (as in septic shock) with global perfusion being normal or even elevated. Regardless of cause or severity, all forms of shock have the commonality of perfusion inadequate to meet metabolic demands at the cellular level. Decreased organ perfusion leads to tissue hypoxia, anaerobic metabolism, activation of the inflammatory cascade, and eventually organ dysfunction. The ultimate consequences of shock depend on the degree and duration of hypoperfusion, the number of organs affected, and the presence of prior organ dysfunction. The challenges to the intensivist are identifying the hypoperfused state, diagnosing its cause, and rapidly restoring cellular perfusion.

PHYSIOLOGY

Significant progress has been made in elucidating the cellular basis for shock. Although low blood pressure and other vital sign derangements were previously thought to be sufficient to cause shock, they are now recognized as being signs of a complex physiologic cascade of events. The delivery and consumption of oxygen at the mitochondrial level, as well as the adequate removal of cellular waste products, is of paramount importance to survival. Cellular hypoxia leads to local vasoconstriction, thrombosis, anaerobic glycolysis, release of superoxide radicals, accumulation of pyruvate and lactate, and intracellular acidosis. The severity of a patient's acidemia, demonstrated by elevated base deficit or lactate levels, correlates with the lethality of shock [7].

In patients who experience such an anaerobic insult, injured tissues and damaged cells release a variety of intracellular mediators which initiate the proinflammatory cascade. Cytokines are small polypeptides and glycoproteins produced by a variety of immunologic cells that are responsible for many of the sequelae seen during shock. Tumor necrosis factor alpha (TNF-α) is one of the earliest cytokines released and is a product of monocytes, macrophages, and T-cells. TNF-α levels rise after a variety of cellular insults and cause hypotension, procoagulant activity, muscle breakdown, catabolism and cachexia. TNF-α levels have been seen to correlate with mortality in animal models of hemorrhagic shock [8]. Produced by macrophages and endothelial cells, interleukin-1 (IL-1) has similar effects, producing fever and anorexia. Activated T-cells produce interleukin-2 which augments cell mediated immunity. Interleukin-6, together with IL-1, mediates the acute phase response to injury and may have a role in the development of acute lung injury. Interleukin-8 is chemotactic for neutrophils and interleukin-12 has a role in cell-mediated immunity by promoting the differentiation of T-helper 1 cells. A variety of "anti-inflammatory" cytokines such as growth hormone interleukin-4, interleukin-10, interleukin-13, soluble TNF receptors (sTNFR), and IL-1 receptor antagonists (IL-1ra) are simultaneously released in an attempt to counterbalance the proinflammatory cascade.

These proinflammatory and counter-regulatory substances may lead to processes that may not be in the best interest of the patient in shock. The body's (mal)adaptive response to the primary injury or inciting event may cause secondary injury to previously unaffected cells and organs leading to impaired perfusion, cellular death, and organ dysfunction. This systemic inflammatory response syndrome, if left unabated, may result in the multiple organ dysfunction syndrome, a common cause of shock-related morbidity and mortality.

IL-1 also activates the patient's hypothalamopituitary axis (HPA) as well as the neuroendocrine response to critical illness. HPA activation releases adrenocorticotrophic hormone (ACTH) that acts on the adrenal gland to stimulate

glucocorticoid (cortisol) production. Appropriate adrenocortical response to shock is essential for patient survival. Relative adrenal insufficiency during critical illness is a commonly underappreciated reason for a patient's failure to respond to resuscitative interventions [9]. Vasopressin (antidiuretic hormone [ADH]) is cosecreted from the posterior pituitary and potentiates the effect of ACTH. In addition to its primary osmoregulatory role in resorption of water from the nephron's collecting duct, ADH is also a potent vasoconstrictor, improving systemic perfusion, and promoting gluconeogenesis and glycolysis to provide much needed metabolic substrates.

The neuroendocrine response to shock involves many counter-regulatory substances. Epinephrine and norepinephrine are produced from the adrenal medulla and synapses of the sympathetic nervous system respectively. β-Adrenergic stimulation results in increased heart rate and contractility, and α-adrenergic stimulation increases systemic vascular resistance and blood pressure through peripheral vasoconstriction. Blood is thus shunted from less essential organs preserving flow to the heart and brain. Sympathetic stimulation also causes venoconstriction accelerating venous return to the central circulation. Through their metabolic effects, catecholamine secretion contributes to stress induced hyperglycemia, a common problem during critical illness. The renin angiotensin system is activated resulting in the release of angiotensin-II (AT-II), another potent vasoconstrictor and stimulus for aldosterone secretion. Aldosterone promotes salt and water conservation at the level of the distal renal tubule in an attempt to preserve intravascular volume. It also regulates acid-base and potassium homeostasis. Glucagon is produced by the pancreatic alpha islet cells and, unlike insulin, has a catabolic role. Release of many of these substances also leads to decreased levels of circulating insulin. The resultant catabolic state characterized by insulin resistance, hyperglycemia, lipolysis, free fatty acid formation, ketogenesis, erosion of lean body mass and negative nitrogen balance may last for weeks to months.

CLASSIFICATION

Shubin and Weil's classic paper distinguished the various forms of shock with respect to cardiovascular parameters [10]. Four categories of inadequate systemic perfusion were described: (a) hypovolemic, (b) obstructive, (c) cardiogenic, and (d) distributive. Although new etiologies of shock (e.g., adrenal insufficiency of critical illness) have recently received significant attention, they are easily placed into one of these physiologic descriptions.

Hypovolemic Shock

Hypovolemic shock is the most common form of shock. Almost all forms include some component of hypovolemia as a result of decreased intravascular volume or "preload." The sympathetic response to reduced preload is arterial vasoconstriction, diverting blood from the splanchnic viscera, skin, and skeletal muscle. Physical findings include cold clammy skin, tachypnea, tachycardia, and low urinary output, all a result of either hypovolemia or compensatory mechanisms.

Hypovolemic shock is stratified into four classes based on the degree of circulating volume loss (Table 157.1). It is important to recognize that significant blood volume may be lost in the absence of any clinical signs. Compensatory mechanisms allow systemic blood pressure to be maintained and a well-compensated patient may display tachycardia as the only objective clinical abnormality, even with a blood volume loss of up to 30%. Hypovolemic shock may be further subclassified as either hemorrhagic or nonhemorrhagic. Hemorrhagic shock may be visibly apparent (external blood loss from traumatic injury) or occult (chronic gastrointestinal hemorrhage). Emphasis on hemorrhage control rather than simply volume replacement is an essential difference in the management of hemorrhagic shock [11,12]. Nonhemorrhagic hypovolemic shock is seen in a number of pathologic states and may be caused by absolute loss of total body fluid volume and/or migration of acellular fluid from the intravascular to the interstitial compartment (third spacing). Third spacing of fluid occurs predictably in severe illnesses such as pancreatitis, small bowel obstruction, and burns. Volume depletion may also occur as a consequence of uncompensated gastrointestinal, urinary, or evaporative losses. It is imperative that the intensivists focus on resuscitation of the patient's intravascular volume as opposed to total body volume. Failure to do so will uniformly result in under-resuscitation and poor patient outcome.

Obstructive Shock

Obstructive forms of shock are those in which the underlying pathology is a mechanical obstruction to normal cardiac output (CO) with a resulting diminution in systemic perfusion. Cardiac tamponade is an example of obstructive shock. A small amount of fluid (usually less than 200 mL) within a noncompliant pericardium may produce significant myocardial compression [13]. Clinical signs of tamponade include jugular venous distention and a central venous pressure (CVP) waveform

TABLE 157.1

CLASSIFICATION OF SHOCK[a]

	Class I	Class II	Class III	Class IV
Blood loss (mL)	Up to 750	750–1,500	1,500–2,000	≥2,000
Blood loss (% blood volume)	Up to 15	15–30	30–40	≥40
Pulse rate	<100	>100	>120	≥140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal/increased	Decreased	Decreased	Decreased
Capillary refill	Normal	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Urinary output (mL/h)	30 or more	20–30	5–15	Negligible
Central nervous system	Slightly anxious	Anxious	Anxious, confused	Confused, lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

[a]Estimates based on a 70-kg male.
Modified from Committee on Trauma of the American College of Surgeons: *Advanced Trauma Life Support for Doctors*. Chicago, American College of Surgeons, 2008, p 61.

demonstrating a rapid "x" descent and a blunted "y" descent due to inability of the heart to fill during diastole. Pulsus paradoxus, an exaggerated fluctuation in arterial pressure caused by changes in intrathoracic pressure during respiration, may be present. Formal echocardiography is helpful in making the diagnosis although recent advances in the use of bedside ultrasonography by noncardiologists have demonstrated excellent sensitivity and rapid performance of the examination [14].

Pulmonary venous thromboembolism is another example of obstructive shock and may present as profound circulatory collapse. CO is restricted either by mechanical obstruction of the pulmonary arterial tree or by pulmonary hypertension induced by release of secondary mediators. Additional findings include elevated CVP and pulmonary hypertension, but normal pulmonary artery occlusion pressure (PAOP). Through similar mechanisms, venous air embolism can completely obstruct pulmonary arterial blood flow, with ensuing cardiac arrest. Central hemodynamics mimic those of pulmonary embolism. Although numerous causes exist, of greatest concern are the placement and removal of central venous catheters and surgical procedures in which the operative site is more than 5 cm above the right atrium [15]. Venous air embolism is diagnosed by auscultation of the classic "mill wheel" heart murmur. Immediate placement of the patient in a head-down, left lateral decubitus position is advocated, as are attempts to aspirate air from the right ventricle through a central venous catheter.

Finally, tension pneumothorax may cause shock through obstruction of venous return. Elevated intrapleural pressure collapses intrathoracic veins resulting in inadequate venous filling. Tension pneumothorax should be diagnosed by physical examination and not by radiography. Needle decompression often restores venous filling sufficiently until a thoracostomy tube can be placed.

Cardiogenic Shock

In cardiogenic shock, the underlying defect is primary ventricular pump failure, the most common cause of coronary artery disease related mortality. The foundations of ventricular failure include (a) myocardial infarction with loss of myocardium, (b) reduced contractility (cardiomyopathy), (c) ventricular outflow obstruction (aortic stenosis or dissection), (d) ventricular filling anomalies (atrial myxoma, mitral stenosis), (e) acute valvular failure (aortic or mitral regurgitation), (f) cardiac dysrhythmias, and (g) ventriculoseptal defects. Most often, cardiogenic shock is a direct or indirect consequence of acute myocardial infarction.

Cardiogenic shock due to left ventricular infarction suggests that more than 40% of the left ventricle is involved [16]. On physical examination, signs of peripheral vasoconstriction are evident and oliguria is common. The typical hemodynamic profile includes systemic hypotension with decreased CO and elevated PAOP. Physical examination findings of pulmonary and peripheral edema as well as hepatomegaly may suggest volume overload, but are commonly due to third spacing of fluid due to shock with relative intravascular volume depletion being present. In such situations, hemodynamic monitoring using echocardiography or a volumetric pulmonary artery catheter may provide additional diagnostic information clarifying the patient's true volume status.

Right ventricular dysfunction as a consequence of inferior wall myocardial infarction carries a better prognosis than left-sided failure. Diagnosis may be suggested by elevated right ventricular diastolic pressure with decreased pulmonary artery pressure [17]. Hypotension caused by right-sided heart failure must be distinguished from left-sided failure because of the significant differences in their management. Shock from right-sided failure is corrected by volume resuscitation to maintain right ventricular preload while left-sided failure is treated by volume restriction to reduce myocardial work. If inotropes are indicated, agents that do not increase pulmonary vascular resistance should be chosen [18].

Dysrhythmias are another source of cardiogenic shock. In addition to malignant dysrhythmias, such as ventricular fibrillation, atrial dysrhythmias such as atrial fibrillation or flutter as well as supraventricular tachycardia are common in the critically ill and may result in shortened diastolic filling time with a profound decrease in CO.

Distributive Shock

The classic hemodynamic profile of septic shock (high CO and systemic hypotension) has prompted some clinicians to institute antimicrobial therapy and search for an infectious source in any patient who exhibits these cardiac parameters. Such hyperdynamic patterns, however, are seen in non-infectious conditions as well including anaphylaxis, spinal cord injury, and severe liver dysfunction. The term distributive shock, rather than septic shock, is therefore used to account for these dissimilar diseases with a common hemodynamic picture.

The management of septic shock remains a major challenge to the intensivist [1–3]. A milieu of inflammatory cytokines, bacterial factors, and complement and coagulation activation combine to induce the complex hemodynamic pattern characteristic of septic shock. In most forms of shock, illness leads to a low CO state with elevated systemic vascular resistance (SVR) and reduced mixed venous oxygen saturation (SvO_2). Early septic shock, however, is manifested by normal-to-low cardiac filling pressures, increased CO, decreased SVR, and increased SvO_2 [19]. Despite elevated systemic blood flow and oxygen delivery (DO_2), abnormalities exist in tissue oxygen extraction at the cellular level, perhaps through disruption of normal mitochondrial metabolic pathways [20,21]. Sepsis-induced myocardial depression may be demonstrated through decreased ejection fraction, right ventricular dysfunction, and left ventricular dilation. In the later stages of septic shock, cardiac function deteriorates with the patient's hemodynamic status mimicking that of cardiogenic shock with decreased CO and increased SVR [22].

Anaphylaxis represents another form of distributive shock in which histamine-mediated vasodilatation occurs. The most common causes are medications, insect envenomations, blood products, radiographic contrast media, and food allergies [23]. Reactions severe enough to result in shock occur shortly after exposure to the offending agent. Physical findings include a dermatologic reaction (erythema, urticaria) and obstructive respiratory processes. Occasionally, the reaction is severe enough to produce shock through myocardial depression.

Neurogenic shock, another form of distributive shock, occurs as a result of upper thoracic spinal cord injury with hypotension, bradycardia, and warm, dry skin due to loss of sympathetic vascular tone. Although euvolemic, patients demonstrate relative hypovolemia due to vasodilatation of the intravascular space. If hypotension does not respond to volume resuscitation, it may be treated with vasopressors and any bradycardia may be corrected with atropine. In the trauma patient, hemorrhage should always be excluded before attributing shock to a neurogenic source [24].

Over the last decade, endocrine insufficiency as a result of critical illness has been recognized as an underappreciated cause of distributive shock. This relative adrenal insufficiency may worsen the impact of the various shock states as the patient is unable to respond appropriately to the stress of their critical illness [25,26]. Corticosteroid supplementation in such

patients can significantly improve systemic perfusion as well as reduce the patient's requirement for vasopressor support.

PHYSIOLOGIC MONITORING

Vital sign derangements are typically the first indication that a shock state is present. Normalization of such parameters signifies that the patient is appropriately responding to resuscitative therapy. Physiologic monitoring is thus essential to both the diagnosis and management of shock. Such monitoring typically begins with the use of routine vital signs, but may progress to the application of invasive monitoring techniques.

Vital Signs

The diagnosis of shock was originally based on abnormalities in a patient's vital signs. Until the late 1960s, the presence of tachycardia and hypotension was considered synonymous with shock. Over time, it became apparent that normalization of heart rate, blood pressure, temperature, and urinary output was not necessarily sufficient to reverse a patient's shock state. Critically ill patients continued to have a high incidence of multiple organ failure and mortality despite seemingly adequate resuscitation based on restoration of vital signs to "normal." Shock is therefore defined by the adequacy of end-organ perfusion rather than derangements in vital signs alone. Nevertheless, these physiologic parameters remain the foundation for the initial recognition that shock is present.

Heart Rate

Alterations in heart rate are common during shock. Tachycardia is most common and is usually a direct effect of intravascular volume loss in where heart rate increases to maintain adequate CO and DO_2 to tissues. These increases may become pathologic if inadequate diastolic filling time results in decreased stroke volume. Tachycardia can be used to predict the presence of intravascular volume depletion and its resolution to suggest volume resuscitation adequacy [27]. Decreased heart rate, in response to a volume challenge, can be a simple and useful test for diagnosing hypovolemia.

Bradycardia is usually representative of severe physiologic derangement and impending cardiovascular collapse. Its presence in a critically ill patient demands immediate attention. Patients receiving beta-blocker therapy or with high spinal cord injuries or pacemakers may not be able to increase their heart rate and compensate for their shock. Patients with an inappropriately low heart rate and inadequate CO will benefit from increasing heart rate by withholding beta-blocker therapy, use of chronotropic medications, or reprogramming their pacemakers to a higher rate.

Blood Pressure

Hypertension is an uncommon finding in shock. Patients are typically hypotensive due to the presence of hypovolemia, decreased cardiac contractility, or systemic vasodilatation. Normotension should be restored as quickly as possible to improve tissue perfusion and oxygen delivery at the cellular level. Blood pressure may be measured either noninvasively or invasively. Both techniques are subject to certain mechanical and physiologic measurement errors, or "dynamic response artifacts," that can result in inappropriate therapy if unrecognized by the clinician [28]. Because of these intrinsic monitoring errors, systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements may vary widely from one measurement technique to another. The mean arterial pressure (MAP), however, will remain fairly consistent regardless of the measurement method and any artifact present. As a result, MAP should be used to titrate resuscitative therapies rather than SBP or DBP. MAP is calculated as

$$MAP = [SBP + 2(DBP)]/3$$

Temperature

Patient temperature, although not indicative of either the presence or absence of shock, may help define the cause and can have significant prognostic value [29,30]. The presence of hypothermia (core body temperature less than 96.8°F or 36.0°C) suggests severe physiologic derangement and has a significant impact on patient survival [31]. Hypothermia places the patient at risk for cardiac dysrhythmias, acute renal failure, and refractory coagulopathy [32]. Although hypothermia reduces metabolic activity of the body, rewarming significantly increases global metabolic demands and oxygen consumption ($\dot{V}O_2$). Such demands may exceed the patient's capacity to deliver oxygen to the cells, resulting in an oxygen transport imbalance. Care must be taken to ensure adequate DO_2 and tissue perfusion during rewarming. Because of its significant morbidity and mortality, nontherapeutic hypothermia should be avoided or rapidly corrected in most critically ill patients [29,30].

Urine Output

Inadequate renal blood flow results in decreased urinary output. Oliguria is one of the earliest signs of inadequate perfusion at the tissue level. Worsening renal function is an important indicator of the presence of shock. Decreases in urine output as a result of hypovolemia are seen before changes in heart rate or blood pressure (Table 157.1). Improvements in urine volume in response to fluid loading can guide shock resuscitation as long as confounding factors are not present (e.g., diabetes insipidus, diabetic ketoacidosis, and diuretic therapy).

Pulse Oximetry

Technologic advances in the 1970s and 1980s led to the widespread introduction of pulse oximetry as the "fifth" vital sign [33]. Pulse oximetry is now routinely used in the critically ill as a noninvasive method of continuously monitoring arterial oxygen saturation. This addition to the traditional four vital signs serves two purposes. First, it provides an early warning of hypoxemia, allowing corrective interventions to be made. Second, it can be used as an endpoint in the resuscitation of patients and in the assessment of oxygen transport balance.

Hemodynamic Monitoring

In 1970, Swan and Ganz introduced the flow-directed pulmonary artery catheter, allowing clinicians to measure pulmonary artery pressures at the bedside [34]. In 1972, addition of a temperature thermistor provided the ability to calculate CO. These advancements provided clinicians with the ability to assess a variety of new hemodynamic parameters evaluating patient preload, contractility, and afterload. In the 1980s, continuous mixed venous oximetry was added as the importance of DO_2, $\dot{V}O_2$, and oxygen transport balance in the diagnosis and management of the shock states became clear. By the early 1990s, catheters capable of calculating right ventricular volumes became available, further improving preload assessment. Current pulmonary artery catheters continuously assess hemodynamic and oxygen transport variables providing the clinician with minute-by-minute assessments of cardiopulmonary function by which to guide resuscitation. Although pulmonary artery catheterization is performed with much less frequency than in years past, it remains an important

monitoring technology for the most critically ill patients with shock and has recently been demonstrated to improve patient outcome when used in a goal-directed fashion [35,36]. A variety of other hemodynamic monitoring techniques have been developed including arterial pressure wave contour analysis, esophageal Doppler, and transesophageal echocardiography among others. Regardless of the method by which hemodynamic data is obtained, a thorough understanding of the available hemodynamic and oxygenation variables is essential if resuscitative therapy is to improve patient outcome from shock (Tables 157.2 and 157.3) [37].

Pressure and Pressure-Derived Variables

Pressure variables form the foundation for physiologic monitoring in shock assessment. It is important to recognize, however, that the absolute value of any single pressure variable is not as important as the trend, calculated variables, and perfusion pressures that may be identified using this pressure.

TABLE 157.2

HEMODYNAMIC VARIABLES

Variable (abbreviation)	Unit	Normal range
Measured variables		
Systolic blood pressure (SBP)	mm Hg	90–140
Diastolic blood pressure (DBP)	mm Hg	50–90
Systolic pulmonary artery pressure (PAS)	mm Hg	15–30
Diastolic pulmonary artery pressure (PAD)	mm Hg	4–12
Pulmonary artery occlusion pressure (PAOP)	mm Hg	2–15
Central venous pressure (CVP)	mm Hg	0–8
Heart rate (HR)	beats/min	Varies by patient
Cardiac output (CO)	L/min	Varies by patient
Stroke volume (SV)	mL/beat	Varies by patient
Right ventricular ejection fraction (RVEF)	Fraction	0.40–0.60
Calculated variables		
Mean arterial pressure (MAP)	mm Hg	70–105
Mean pulmonary artery pressure (MPAP)	mm Hg	9–16
Cardiac index (CI)	$L/min/m^2$	2.8–4.2
Stroke volume index (SVI)	$mL/min/m^2$	30–65
Systemic vascular resistance index (SVRI)	Dyne/sec/cm^5	1,600–24,00
Pulmonary vascular resistance index (PVRI)	Dyne/sec/cm^5	250–340
Left ventricular stroke work index (LVSWI)	g × m/m^2	43–62
Right ventricular stroke work index (RVSWI)	g × m/m^2	7–12
Coronary perfusion pressure (coronary PP)	mm Hg	> 50
Cerebral perfusion pressure (cerebral PP)	mm Hg	50–70
Abdominal perfusion pressure (APP)	mm Hg	> 60
Right ventricular end-diastolic volume index (RVEDVI)	mL/m^2	80–120
Global end-diastolic volume index (GEDVI)	mL/m^2	600–800
Stroke volume variation (SVV)	%	< 10
Pulse pressure variation (PPV)	%	< 10
Body surface area (BSA)	m^2	Varies by patient

TABLE 157.3

OXYGENATION VARIABLES

Variable (abbreviation)	Unit	Normal range
Measured variables		
Arterial oxygen tension (PaO_2)	mm Hg	70–100
Arterial carbon dioxide tension ($PaCO_2$)	mm Hg	35–50
Arterial oxygen saturation (SaO_2 or SpO_2)	Fraction	0.92–0.98
Mixed venous oxygen saturation (SvO_2)	Fraction	0.65–0.75
Mixed central venous oxygen saturation ($ScvO_2$)	Fraction	0.70–0.80
Mixed venous oxygen tension (PvO_2)	mm Hg	35–40
Hemoglobin (Hgb)	g/dL	13–17
Calculated variables		
Oxygen delivery index (DO_2I)	$mL/min/m^2$	500–650
Oxygen consumption index ($\dot{V}O_2I$)	$mL/min/m^2$	110–150
Arterial oxygen content (CaO_2)	mL O_2/dL blood	16–22
Venous oxygen content (CvO_2)	mL O_2/dL blood	12–17
Arterial–venous oxygen content difference ($Ca–vO_2$)	mL O_2/dL blood	3.5–5.5
Oxygen utilization coefficient (OUC)	Fraction	0.25–0.35

Mean Arterial and Mean Pulmonary Arterial Pressure. MAP has been discussed previously. Mean pulmonary arterial pressure (MPAP) is the equivalent pressure for the pulmonary circuit (Fig. 157.1) and is calculated using pulmonary arterial systolic (PAS) and diastolic (PAD) pressure:

$$MPAP = [PAS + 2(PAD)]/3$$

Mean pressures should be used to guide decision making and resuscitative therapy whenever possible as they are less

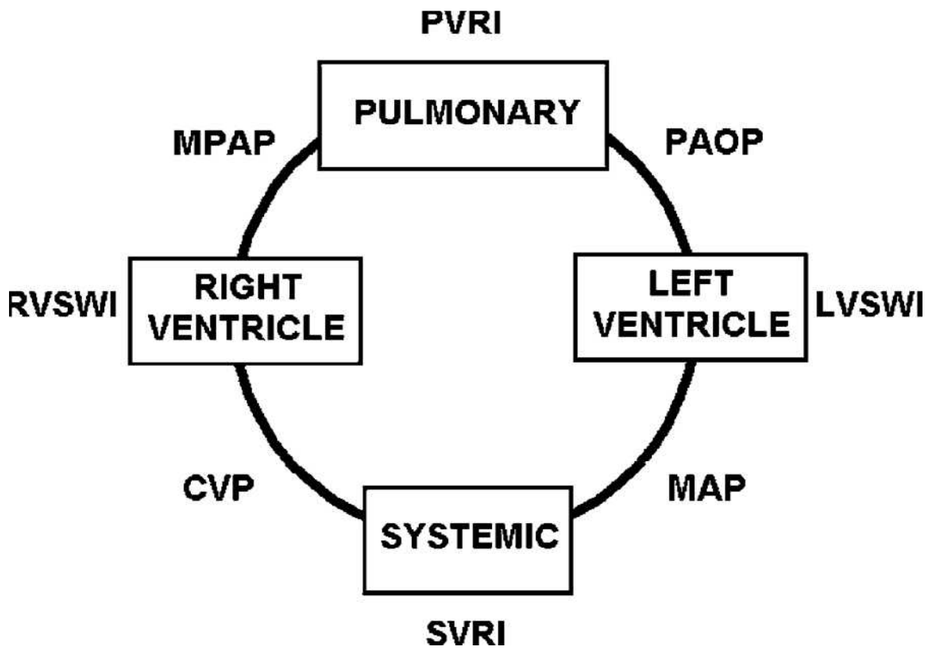

FIGURE 157.1. Hemodynamic calculations. PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke work index.

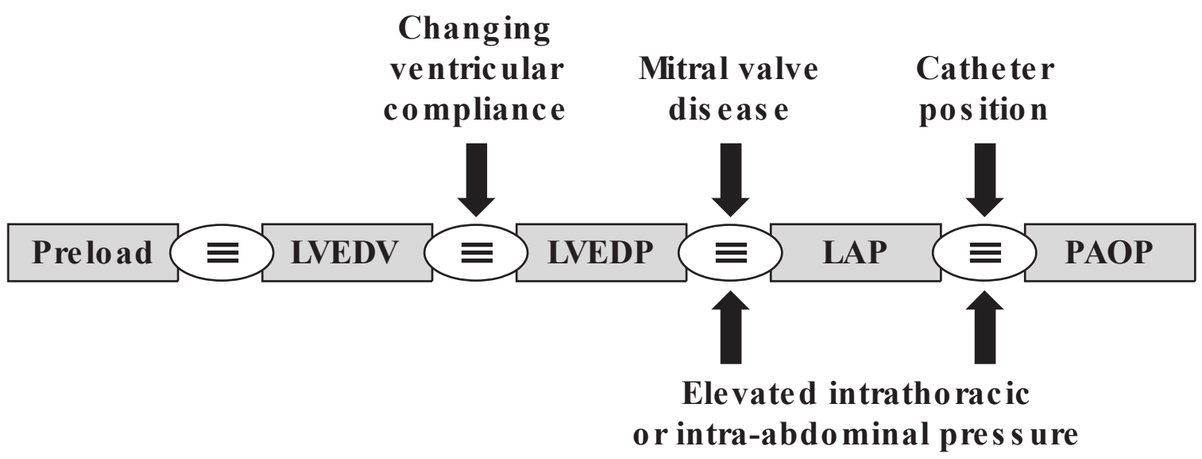

FIGURE 157.2. The "PAOP assumption": Why intracardiac filling pressures do not accurately estimate preload status? LVEDV, left ventricular end-diastolic volume; LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure; PAOP, pulmonary artery occlusion pressure. [Adapted from Cheatham ML: Right ventricular end-diastolic measurements in the resuscitation of trauma victims. *Int J Crit Care* 7:165–176, 2000, with permission.]

subject to monitoring artifacts. They are also essential components to calculate vascular resistance and cardiac work.

Pulmonary Artery Occlusion and Central Venous Pressure. Fluid administration is an essential element in the initial resuscitation of almost all forms of shock. Intracardiac-filling pressure measurements such as PAOP or "wedge" and CVP are commonly used to estimate intravascular volume or "preload." Preload, by the Frank–Starling Law, is defined in terms of myocardial fibril length at end-diastole. Because this is clinically immeasurable, several assumptions are made to use PAOP to clinically assess the preload status of the left ventricle (Fig. 157.2). These assumptions are frequently invalid in critically ill patients due to changing ventricular compliance caused by a variety of factors. As a result, PAOP measurements should be carefully considered as estimates of intravascular volume status in the patient with shock [38–40]. In fact, reliance on PAOP measurements for preload assessment in critically ill patients may lead to inappropriate interventions in more than 50% of patients [41]. The trend rather than the absolute value of such measurements in response to therapeutic interventions is of greater value. The optimal PAOP is that value which, through careful evaluation of the patient's hemodynamic status, is determined to optimize systemic perfusion (CO) and cellular oxygenation (DO_2, $\dot{V}O_2$). For similar reasons, absolute CVP measurements do not accurately portray left ventricular volume status or ventricular function [38–41]. As with PAOP, the trend of CVP measurements in response to therapeutic measures may be of value.

Perfusion Variables

The importance of adequate end-organ perfusion in correcting the shock state cannot be overemphasized. The following perfusion variables are easily calculated and represent important resuscitation endpoints in the critically ill.

Coronary Perfusion Pressure. Maintaining adequate coronary perfusion pressure (PP) should be a primary goal in the resuscitation of any patient in shock. Patients with preexisting coronary artery disease may have marginal myocardial blood flow, which is only worsened by inadequate systemic perfusion during shock. Coronary PP is calculated as the pressure change across the coronary artery during maximal blood flow:

$$\text{coronary perfusion} = \text{pressure change across the coronary artery}$$
$$\text{coronary PP} = \text{DBP} - \text{PAOP}$$

The goal should be to maintain coronary PP greater than 50 mm Hg. Failure to maintain this level of perfusion increases the risk for myocardial ischemia and infarction. Note that DBP and not SBP is the critical determinant of coronary perfusion as maximal myocardial blood flow occurs during diastole. PAOP estimates myocardial wall tension and resistance to perfusion by approximating end-diastolic pressure in the left ventricle.

Cerebral Perfusion Pressure. Monitoring cerebral perfusion pressure is important in the head-injured patient with increased intracranial pressure (ICP) [42]. Because the brain is enclosed within the skull with little room for expansion, increases in ICP and development of cerebral edema can have significant and detrimental effects on cerebral blood flow and oxygenation. Monitoring of ICP is an important component of the hemodynamic monitoring of patients with brain injury and shock. Cerebral PP is calculated as the pressure change across the brain:

$$\text{cerebral perfusion} = \text{pressure change across the brain}$$
$$\text{cerebral PP} = \text{MAP} - \text{ICP (or CVP, whichever is higher)}$$

The goal should be to maintain a cerebral PP of 50 to 70 mm Hg [42]. This may be accomplished by either increasing MAP (using a vasopressor such as norepinephrine) or decreasing intracerebral volume (through the use of mannitol or hypertonic fluids), thereby decreasing ICP. Maintenance of a cerebral PP > 70 mm Hg does not appear to provide a survival benefit and may lead to potentially detrimental over-resuscitation.

Abdominal Perfusion Pressure. Analogous to coronary and cerebral PP, abdominal perfusion pressure (APP) has been identified as a valuable parameter in the resuscitation of patients with elevated intra-abdominal pressure (IAP), a condition present in over half of all ICU patients [43,44]. IAP is most commonly determined as intravesicular or "bladder" pressure by transducing the patient's indwelling urinary catheter [45,46]. APP is calculated as the pressure change across the abdominal organs:

$$\text{abdominal perfusion} = \text{pressure change across the abdominal organs}$$
$$\text{APP} = \text{MAP} - \text{IAP}$$

Failure to maintain APP ≥ 60 mm Hg has been found to discriminate between survivors and nonsurvivors [43]. Maintenance of adequate APP through a balance of judicious fluid resuscitation and application of vasoactive medications has been demonstrated to reduce the incidence of acute renal failure [47].

Blood Flow and Flow-Derived Variables

Critically ill patients with shock and systemic malperfusion frequently benefit from calculation of blood flow-related variables such as CO and stroke volume (SV). Flow-related variables are used with pressure variables to calculate vascular resistance and estimate the work performed by the left and right ventricles. Such advanced hemodynamic monitoring should be implemented whenever a patient fails to respond to resuscitation as expected.

Interpatient variability makes it difficult to assign a normal range to flow-derived variables. What might be an adequate CO for a 50-kg woman is inadequate for a 150-kg man. To normalize these measurements and allow comparison from patient to patient, flow-derived variables are indexed to body surface area (BSA), obtained from a nomogram. Indexed variables, such as cardiac index (CI) and stroke volume index (SVI), are more meaningful because normal ranges aid in interpretation.

All flow-derived hemodynamics should be indexed to facilitate comparison with accepted normal ranges.

Cardiac Index and Stroke Volume Index. CI is the total blood flow from the heart (in liters per minute) divided by BSA. SVI is the volume of blood ejected from the heart per beat, divided by BSA:

$$CI = \text{cardiac output/BSA}$$
$$SVI = CI/\text{heart rate}$$

Most shock states have a decreased CI as a result of intravascular volume depletion, poor underlying cardiac pump function, increased vascular resistance, or a combination of these factors. To maintain CI, tachycardia is the usual response to inadequate preload and a low SVI. Appropriate therapy is to restore intravascular volume and increase SVI, thus improving CI. An increased CI may be seen in early septic shock, but may also be seen with other nonshock hyperdynamic states, such as cirrhosis, pregnancy, and high-performance athletes.

Systemic Vascular Resistance Index/Pulmonary Vascular Resistance Index. According to Ohm's law, the resistance of an electrical circuit is equal to the voltage difference across the circuit divided by the current. A simplified view of the circulatory system can be likened to an electrical circuit in which the resistance across the systemic or pulmonary vascular beds is calculated using Ohm's law (Fig. 157.1):

$$\text{Resistance} = \text{voltage difference/current}$$
$$\text{Vascular resistance} = \text{pressure change/total blood flow}$$
$$SVRI = \frac{\text{change in pressure across the systemic circuit (mm Hg)}}{\text{total blood flow (L/min/m}^2\text{)}}$$
$$SVRI \text{ (in dynes/sec/cm}^5\text{)} = (MAP - CVP)(79.9)/CI$$
$$PVRI = \frac{\text{change in pressure across the pulmonary circuit (mm Hg)}}{\text{total blood flow (L/min/m}^2\text{)}}$$
$$PVRI \text{ (in dynes/sec/cm}^5\text{)} = (MPAP - PAOP)(79.9)/CI$$

The constant, 79.9, is used to convert mm Hg · L per minute to the more physiologic units of dynes per seconds per · cm^5.

Increased SVRI is commonly seen in obstructive, hypovolemic, late septic, and cardiogenic shock. Systemic resistance may also rise in nonshock states such as pheochromocytoma (secondary to increased endogenous catecholamine output). Decreased SVRI is common in distributive shock states (neurogenic, early septic, endocrine shock). Vasodilators such as sodium nitroprusside, nitroglycerin, and other antihypertensives reduce SVRI.

Increased PVRI is indicative of pulmonary hypertension and may be classified as being either primary or secondary. Primary pulmonary hypertension is an intrinsic lung disease developing over many years and typically refractory to treatment. Secondary pulmonary hypertension may develop as a result of acute respiratory distress syndrome, application of positive end-expiratory pressure (PEEP), or development of mitral or aortic stenosis. Treatment of pulmonary hypertension begins with institution of increased inspired oxygen fractions due to oxygen's effect as a potent pulmonary vasodilator. Nitroglycerin and morphine sulfate also are helpful in the acute treatment of pulmonary hypertension. Decreased PVRI occurs in the setting of various shock states. Treatment is rarely instituted to specifically increase PVRI alone.

Perfusion pressure and vascular resistance determine total blood flow to an organ, but absolute values of these determining factors do not define the shock state. For example, a high vascular resistance is commonly compensatory for reduced systemic perfusion pressure. The same numeric value of high resistance may contribute to organ dysfunction when it is so high that perfusion pressure cannot overcome it. When organ blood flow is maldistributed, as in septic shock or abdominal compartment syndrome, multiple organ dysfunction may occur despite normal systemic perfusion pressures. It is also important to recognize that vascular resistance numbers are calculated and are inversely proportional to CI. Therefore, therapy should usually be directed at enhancing CI in addition to reducing vascular resistance as simply reducing vascular resistance may reduce perfusion pressure.

Ventricular Stroke Work Indices. The ventricular stroke work indices describe how much work the ventricles perform and can identify patients with poor cardiac function. They may also be useful to construct ventricular function curves to assess a patient's response to therapy. As with vascular resistance, the work performed by the heart can also be calculated using the laws of physics. Work is calculated as the force generated multiplied by the distance over which the work is performed. Clinically, the force generated (per area) by each side of the heart is the change in pressure it creates across the ventricle. The distance (per area) is the volume of blood ejected with each beat (SVI) normalized for patient size. Therefore,

$$\text{Ventricular stroke work index} = \text{change in pressure} \times \text{change in volume}$$
$$\text{Left ventricular stroke work index (LVSWI)} = (MAP - PAOP)(SVI)(0.0136)\ (g \cdot m/m^2)$$
$$\text{Right ventricular stroke work index (RVSWI)} = (MPAP - CVP)(SVI)(0.0136)\ (g \cdot m/m^2)$$

The constant (0.0136) converts mm Hg · L/beat · m^2 to g · m/m^2.

Increased LVSWI/RVSWI is relatively uncommon, but may be encountered in patients with ventricular hypertrophy, pulmonary hypertension, or in athletes. Decreased LVSWI/RVSWI is much more common and may be seen in various shock states; heart failure; aortic or mitral stenosis; myocardial depression, ischemia, or infarction; or advanced age. When evaluating decreased ventricular stroke work, it is important to keep in mind that the decreased function may be due to decreased intravascular volume (decreased SVI), changes in vascular resistance (increased MAP or MPAP), or decreased contractility. If preload and afterload remain constant, decreases in stroke work indicate decreases in ventricular contractility.

Volumetric Variables

The clinical accuracy of pressure-based monitoring techniques is limited by a variety of factors including proper catheter positioning, pressure transducer calibration, and pressure waveform interpretation. By the Frank–Starling principle, ventricular preload is defined as myocardial muscle fiber length at end-diastole with the appropriate clinical correlate being end-diastolic volume. As ventricular chamber volume cannot be directly measured, intracardiac filling pressures such as PAOP and CVP have been used as estimates of end-diastolic volume under the erroneous assumption that ventricular compliance remains constant. Ventricular compliance, however, is *constantly* changing in the critically ill, resulting in a variable relationship between pressure and volume. Further, PAOP and CVP must be measured relative to an arbitrary reference point (typically the perceived position of the right atrium) and are subject to the impact of increased intrathoracic and intra-abdominal pressure (as may occur with acute lung injury, PEEP, intra-abdominal hypertension, abdominal compartment syndrome, etc.) (Fig. 157.2). Although attempts may be made to calculate transmural PAOP and CVP values, these estimates are inexact and the level of precision necessary to measure CVP accurately at the bedside is rarely performed [48]. As a result, changes in PAOP and CVP as commonly measured do not directly reflect changes in intravascular volume in the critically ill and may lead

to inappropriate clinical interventions and under-resuscitation [41].

In the 1990s, a new generation of monitoring technologies were introduced that provide volumetric as opposed to pressure-based estimates of hemodynamic function. These included continuous CO, right ventricular ejection fraction (RVEF), and right ventricular end-diastolic volume index (RVEDVI), via a modified pulmonary artery catheter, or global ejection fraction (GEF), global end-diastolic volume index (GEDVI), intrathoracic blood volume index (ITBVI), and extravascular lung water (EVLW) via an arterial catheter using the arterial pulse contour analysis technique. Continuous volumetric monitoring provides a minute-by-minute assessment of patient response to therapeutic interventions, potentially allowing more rapid and effective resuscitation compared to traditional pressure-based monitoring techniques [27,49–52]. Both RVEDVI and GEDVI have been demonstrated to be superior to PAOP and CVP as predictors of preload recruitable increases in CI during shock resuscitation [27,40,41,49–52]. Further, several studies have demonstrated either significantly improved organ perfusion and function or increased patient survival when volumetric resuscitation endpoints are employed [27,49,50]. More recently, arterial pulse contour analysis has been used to measure stroke volume variation (SVV), the variation in beat-to-beat stroke volume during a single respiratory cycle, as well as pulse pressure variation (PPV), the beat-to-beat difference between SBP and DBP. Both of these parameters have been suggested to be valuable predictors of hypovolemia and fluid responsiveness [53]. These advanced hemodynamic monitoring techniques are appropriate for patients with shock who fail to respond appropriately to initial attempts at resuscitation using conventional endpoints.

Oxygen Transport Variables

With recognition of the importance of oxygen delivery (DO_2) and oxygen consumption ($\dot{V}O_2$) in the treatment of the various shock states, monitoring of a patient's oxygen transport balance has become commonplace (Table 157.3). The foremost question in critical care is whether oxygen transport to the tissues is sufficient to meet the demand for oxygen at the cellular level.

Oxygen transport represents the balance between supply and demand. When supply exceeds demand, the cellular oxygen requirements of the body are being met, and normal metabolic processes proceed uninhibited. When oxygen supply equals demand, vital functions may progress normally, but with little physiologic reserve, such that a relatively minor insult can upset the oxygen transport balance. In such a situation, organs that possess a high baseline oxygen extraction, such as the heart, are at significant risk for ischemia. When shock-induced systemic or regional malperfusion exists, oxygen demand exceeds supply, and the available cellular oxygen is inadequate to support normal physiology. Energy must therefore be produced via anaerobic metabolism with production of lactic acid as a by-product. As lactic acid cannot be reutilized in the absence of oxygen, it accumulates leading to metabolic acidosis, cellular injury, and cellular death. Left unchecked, this imbalance in oxygen transport will result in the development of multisystem organ failure and patient death. The role of the intensivist is to recognize oxygen supply imbalances at the cellular level, initiate therapeutic interventions to increase oxygen delivery, prevent further organ dysfunction, ensure adequate physiologic oxygen reserve to cope with acute increases in oxygen demand, and improve patient outcome from shock.

Knowledge of the oxygen transport equations is essential to understanding the pathophysiology and appropriate treatment for the various shock states. Any assessment of oxygen transport begins with the calculation of DO_2 and $\dot{V}O_2$. To accomplish this, the oxygen content of the blood at various points in the systemic and pulmonary circulation must be identified (Fig. 157.3). Central to these calculations are the recognition that (1) oxygen may be either "bound" or "unbound" to erythrocytes, (2) each gram of hemoglobin (Hgb) can carry up to 1.34 mL of oxygen, (3) the solubility of oxygen in blood is 0.0031 mL per dL, and (4) the amount of oxygen carried by Hgb depends upon its saturation.

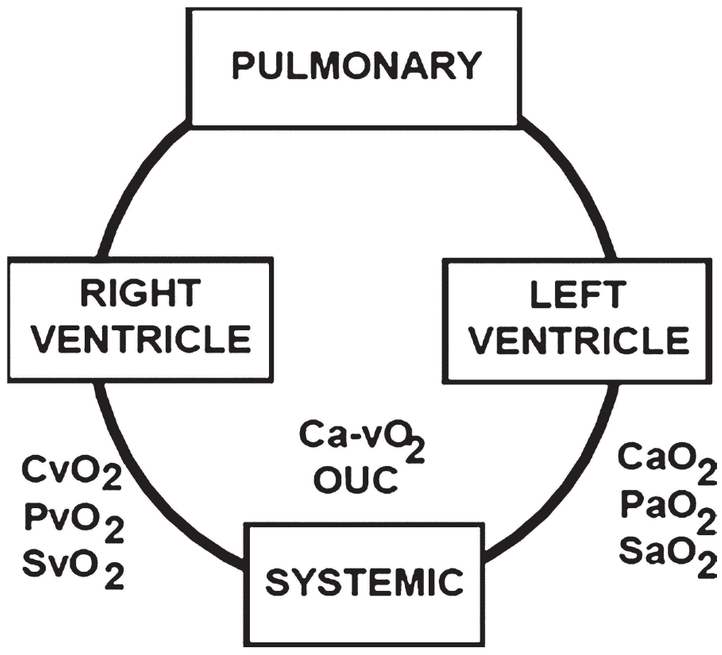

FIGURE 157.3. Oxygenation calculations. CaO_2, arterial oxygen content; PaO_2, arterial oxygen tension; SaO_2, arterial oxygen saturation; CvO_2, venous oxygen content; PvO_2, venous oxygen tension; SvO_2, mixed venous oxygen saturation; $Ca–vO_2$, arterial–venous oxygen content difference; OUC, oxygen-utilization coefficient.

The oxygen content of arterial blood as it leaves the heart may be calculated as:

$$\begin{aligned} CaO_2 &= \text{oxygen bound to arterial Hgb} + \text{oxygen dissolved in arterial blood} \\ &= (1.34 \times \text{Hgb} \times SaO_2) + (PaO_2 \times 0.0031) \end{aligned}$$

In a similar fashion, the oxygen content of venous blood as it returns to the heart may be calculated as:

$$\begin{aligned} CvO_2 &= \text{oxygen bound to venous Hgb} + \text{oxygen dissolved in venous blood} \\ &= (1.34 \times \text{Hgb} \times SvO_2) + (PvO_2 \times 0.0031) \end{aligned}$$

The partial pressure of oxygen in venous blood (PvO_2) is typically 35 to 40 Torr. As a result, for most purposes, the contribution of dissolved oxygen in venous blood is so small as to be clinically insignificant and is often disregarded. The arterial–venous oxygen content difference ($Ca–vO_2$) therefore represents the amount of oxygen extracted by the tissues and organs of the body. It is frequently elevated in shock, due to the increased oxygen demands of injured tissue, and represents an important resuscitation endpoint. The $Ca–vO_2$ is calculated as:

$$\begin{aligned} Ca–vO_2 &= \text{arterial–venous oxygen content difference} \\ &= CaO_2 - CvO_2 \end{aligned}$$

$Ca–vO_2$ is an important indicator of the relative balance between CI and $\dot{V}O_2$. A $Ca–vO_2$ in excess of 5.5 mL per dL of oxygen suggests that CI is inadequate to meet cellular oxygen demands and that anaerobic metabolism and lactic acidosis may result. Maneuvers to improve CI and DO_2 should be performed to meet the patient's cellular oxygen demand and reduce $Ca–vO_2$ to a normal range.

The volume of oxygen delivered from the left ventricle (DO_2) and the amount of oxygen consumed by the organs ($\dot{V}O_2$) provide the clinician with vital information by which to assess the patient's overall oxygen transport balance. DO_2 is determined by two factors: the volume of oxygen in blood

(CaO_2) and the blood flow delivered (CI). Values indexed to BSA allow comparison across patients of differing body habitus, so that

DO_2I = oxygen delivery index
= volume of oxygen pumped from the left ventricle per minute per m^2
= (CaO_2) (CI) (10 dL/L)

$\dot{V}O_2$ is calculated similarly, using $Ca–vO_2$ to account for the oxygen consumed by the body:

$\dot{V}O_2I$ = oxygen consumption index
= volume of oxygen consumed by the body per min per m^2
= volume of oxygen delivered − volume of oxygen returned per minute per m^2
= ($Ca–vO_2$) (CI) (10 dL/L)

One of the most important determinants of tissue DO_2I is Hgb concentration. The optimal Hgb concentration during shock resuscitation remains a topic of significant debate. Although previous clinical trials concluded that a Hgb concentration of 7 g per dL is sufficient and that transfusion to higher levels provides no survival benefit, it must be remembered that hemodynamically unstable patients, including hemorrhagic shock victims, were excluded from the study [54]. Further, patients with recent acute myocardial infarction or unstable angina were felt to require a higher Hgb concentration to ensure adequate DO_2I. More recent studies in hemorrhagic shock patients, however, have demonstrated significantly improved survival among patients resuscitated to a Hgb > 11 g per dL [55]. Recent evidence-based medicine guidelines have advocated higher Hgb levels in patients with myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, lactic acidosis, or closed head injury [2]. Although a subject of continued controversy, the optimal Hgb concentration can appropriately be considered the level that restores a patient's oxygen transport balance while minimizing the potentially detrimental infectious and immunosuppressive effects of allogeneic blood.

Shock Resuscitation Adequacy

Resuscitation of the critically ill patient who has developed one of the shock states is an ongoing process. It requires constant assessment of the patient's response to resuscitative therapy. In the patient whose shock state and oxygen transport balance fail to improve, the administered therapies must be reconsidered and adjusted as necessary to achieve the desired outcome. To guide this dynamic resuscitation, "resuscitation adequacy" endpoints may be employed.

Mixed Venous Oximetry

Continuously measured SvO_2 correlates well with calculated oxygen extraction ratios and represents a valuable endpoint for assessing the adequacy of shock resuscitation [56]. The four factors affecting SvO_2 are (1) SaO_2, (2) Hgb concentration, (3) CO, and (4) $\dot{V}O_2$. Increases in any of the three variables affecting DO_2 (SaO_2, Hgb concentration, and CO) result in an increase in SvO_2, whereas uncompensated increases in $\dot{V}O_2$ result in a decrease in SvO_2. The SvO_2 measured in the proximal pulmonary artery is a global flow-weighted average of the effluent blood from all perfused vascular beds. SvO_2 does not reflect the oxygenation of nonperfused tissues; thus, a normal SvO_2 does not mean that all organs are adequately oxygenated. In the absence of a pulmonary artery catheter, the mixed central venous oxygen saturation ($ScvO_2$) may be measured either intermittently using a venous blood gas drawn from a central venous catheter whose tip is located in the superior vena cava or continuously via a special oximetric central venous catheter [1]. It should be recognized that SvO_2 and $ScvO_2$ are not equivalent measurements with normal $ScvO_2$ values being 0.05 to 0.1 higher than SvO_2.

A low SvO_2 (less than 0.65) virtually always indicates an unfavorable disturbance in the normal balance between DO_2 and $\dot{V}O_2$. Normal or high values of SvO_2 are more difficult to interpret. A normal SvO_2 in a patient with otherwise normal hemodynamics generally indicates a stable condition with a satisfactory oxygen transport balance. A high SvO_2 (greater than 0.75) is difficult to interpret and implies a either a maldistribution of peripheral blood flow, providing some vascular beds with DO_2 in excess of consumption, or the presence of "shunting" in which oxygenated blood is returned to the heart without releasing its bound oxygen. This state of vaso-deregulation is often associated with high-flow states such as cirrhosis, sepsis, pregnancy, and inflammation.

Arterial Lactate

As discussed previously, shock is hypoperfusion resulting in inadequate DO_2 to meet tissue oxygen demand at the cellular level. The resulting oxygen debt forces cells to switch to anaerobic metabolism to make adenosine triphosphate by the inefficient method of glycolysis. The by-products of glycolysis are hydrogen ion, pyruvate, and lactate. If aerobic metabolism is restored through resuscitation and improved tissue DO_2, the excess hydrogen ion is buffered, and both pyruvate and lactate are metabolized to yield adenosine triphosphate. Under continued anaerobic conditions, however, hydrogen ion and lactate accumulate within the cell, resulting in acidosis, injury, and cellular death. Serum lactate levels therefore provide the clinician with an excellent laboratory marker of the presence of anaerobic metabolism as well as resuscitation adequacy.

Elevated serum lactate levels indicate that the patient has sustained a period of inadequate perfusion and oxygenation within the past 6 to 12 hours with the severity of lactic acidosis directly correlating with the severity of the shock insult. If such levels are rising, anaerobic metabolism remains ongoing and the magnitude of resuscitative therapy should be increased. A decreasing lactate level suggests that resuscitation has been adequate and anaerobic metabolism has resolved. Although serum lactate levels identify the presence of anaerobic metabolism, they are not specific in identifying the location of abnormal regional perfusion. Further, profound hypoperfusion can exist despite normal lactate levels when there is inadequate blood flow to ischemic tissues. Some septic patients have increased lactate levels in the absence of hypoperfusion as a result of increased aerobic glycolysis. In this situation, the elevated lactate continues to be significant despite resuscitation and is an indicator of a potentially severe pathologic process. Patients with significant hepatic dysfunction do not clear lactate normally, and will therefore manifest higher lactate levels in the absence of anaerobic metabolism [57].

Elevated lactate concentrations predict an increased mortality rate. The magnitude and duration of the elevation correlate with mortality and reversal of hyperlactatemia suggests a better prognosis. Mortality rates of 24% to 86% are seen if lactate has not normalized by 48 hours [57–61].

Base Deficit

The presence of an elevated base deficit correlates directly with the presence and severity of shock [61–63]. It predicts fluid resuscitation requirements and is a rapidly obtainable monitor of resuscitation adequacy [62]. Further, base deficit normalizes rapidly with restoration of aerobic metabolism, making it a useful physiologic marker by which to guide resuscitation. Base deficit must be interpreted with caution in the patient who has

received exogenous sodium bicarbonate as it will no longer be useful as a predictor of resuscitation adequacy.

Rutherford et al. identified that patients younger than 55 years of age without a head injury who demonstrate a base deficit of −15 mmol per L have a 25% mortality rate [63]. Patients with a head injury or patients older than 55 years without a head injury have a 25% mortality at a base deficit of −8 mmol per L. These authors suggested that base deficit could be used to identify patients in severe shock who might benefit from having operative procedures terminated early (so-called "damage control laparotomy").

Treatment Principles

Patient morbidity and mortality after development of one of the shock syndromes correlates directly with the duration and severity of malperfusion. The intensivist must therefore rapidly diagnose the presence and cause of shock, restore systemic and regional perfusion to prevent ongoing cellular injury, and prevent the development of end-organ failure. The intensivist must command a strong understanding of the various therapeutic options for each of the shock states. Using the hemodynamic variables and calculations previously described, shock resuscitation should focus on assessment of preload, contractility, afterload, and oxygen transport balance with the intent to optimize the patient's end-organ perfusion and cellular oxygenation. In addition, the etiology for the shock state should be investigated to treat and/or correct the underlying cause. This may be simple, as in needle decompression for a tension pneumothorax, or may be complex, as in the treatment of sepsis.

Preload

In almost all shock states, a component of diminished preload, either relative or absolute, exists. Therefore, the initial therapeutic intervention for almost all patients in shock should be a crystalloid bolus of 20 mL per kg with subsequent resuscitation guided by signs of improved organ perfusion: reduction in tachycardia, restoration of normotension, maintenance of adequate urinary output, return of normal mentation, improvement in systemic oxygenation, and/or correction of abnormalities in serum lactate or base deficit. In patients with preexisting cardiopulmonary disease or those who do not respond to resuscitation as expected, invasive hemodynamic monitoring may be of value in achieving these goals.

Over-resuscitation with intravenous fluids should be avoided and can cause acute lung injury, intra-abdominal hypertension, and abdominal compartment syndrome. Although some authors have suggested the use of colloid-based resuscitation to avoid such complications, large-scale clinical trials and meta-analyses have failed to demonstrate a survival advantage to such an approach [64,65]. A subset analysis of the SAFE trial demonstrated an increased mortality in head injured patients who received colloid-based resuscitation [66]. A balanced resuscitation using a combination of crystalloid and colloid reduces the required resuscitation volume and appears to be associated with decreased organ dysfunction and failure [65].

In patients with hemorrhagic shock, blood product transfusions should be considered early in the volume resuscitation phase as increasing evidence from the battlefield has demonstrated improved survival with early, aggressive blood, plasma, and platelet transfusions to restore adequate hemoglobin concentration and normal coagulation [55]. Current evidence suggests that a 1:1:1 ratio of packed red blood cells/plasma/platelets reduces the morbidity and mortality of hemorrhagic shock [67,68].

Contractility

Resuscitative therapy should optimize the patient's heart rate. Although tachycardia may partially compensate for low perfusion, further increases in heart rate may only decrease diastolic filling of the heart and reduce CO. Treatment of pain and anxiety as well as control of supraventricular tachyarrhythmias in the volume-resuscitated patient can improve CO. In bradycardia from neurogenic shock, atropine-induced blockage of parasympathetic stimulation may help ameliorate the hypoperfusion by raising heart rate and CO. Patients taking beta-blockers who have inappropriately low heart rates may benefit from administration of both calcium and glucagon. Those with pacemakers who are unable to raise their own heart rates in response to shock will frequently benefit from resetting their pacemakers to a more physiologically appropriate higher rate.

Contractility agents should be considered only after adequate attempts to improve preload have been made. Dopamine, a naturally occurring catecholamine that is the immediate precursor of norepinephrine, is a widely used agent with a variable dose response. Classically, low rate (0 to 3 µg per kg per minute) or so-called "renal dose" dopamine was advocated to increase glomerular filtration rate, renal blood flow, and urinary output. The clinical benefit of such therapy, however, has been disproven and dopamine's use in this fashion has largely been abandoned [69]. In moderate doses (5 to 10 µg per kg per minute), cardiac contractility and heart rate are increased through stimulation of cardiac beta-receptors. High-dose dopamine therapy (10 µg per kg per minute and higher) results in stimulation of α-adrenergic receptors, elevating systemic blood pressure. Although a valuable tool in improving cardiac performance, dopamine should be used with caution in patients with coronary artery stenosis because of the potential risk of tachycardia and increased myocardial oxygen demand.

Dobutamine is a synthetic catecholamine that also acts on β_1-receptors, but, unlike dopamine, does not directly release norepinephrine. Dobutamine has both chronotropic and systemic vasodilatory effects, reducing afterload and increasing CO in the weakened heart. However, it should be used with caution in hypovolemic, vasodilated states, as it may decrease blood pressure and increase heart rate, leading to reduced systemic perfusion [70].

Norepinephrine is a naturally occurring catecholamine with both α- and β-adrenergic activity. As a potent vasoconstrictor, there is some reluctance to use this agent because of its possible effects on mesenteric and renal blood flow. However, in the setting of an appropriately volume-repleted patient who remains hypotensive, norepinephrine has been shown to be effective and safe and may have beneficial effects on renal function [71]. It should be considered the vasopressor of choice of all but the cardiogenic shock states [2].

Amrinone is a noncatecholamine intravenous inotrope that, like dobutamine, has vasodilatory effects. Its mechanism of action is as a phosphodiesterase-III inhibitor, raising intracellular cyclic adenosine monophosphate levels. In patients with shock due to congestive heart failure, amrinone increases stroke volume without an effect on heart rate. In some patients with hypovolemic shock, its vasodilatory properties preclude its use because of dramatic hypotension.

Afterload

If preload is optimized and hemodynamic goals have still not been met, afterload should be assessed and corrected as needed. The persistently hypotensive patient should not be considered a candidate for afterload reduction. In patients with hypertension or even normotension, however, afterload reduction may allow for improved CO and, hence, improved resuscitation especially in patients with decreased contractility.

Sodium nitroprusside is a commonly used agent with the advantages of rapid onset and short duration, making it ideal

for titration in the hemodynamically labile patient. Nitroprusside acts as both a venous and arterial vasodilator, in essentially equal amounts. However, it should be used with caution in patients with coronary artery disease when concerns of coronary steal and myocardial ischemia exist. Alternatively, intravenous nitroglycerin may be used. Although primarily affecting venous capacitance, nitroglycerin also decreases arterial resistance and may improve CO. Angiotensin-converting enzyme–inhibiting agents may also be of significant value in reducing afterload in the normovolemic patient with poor cardiac function.

Afterload may also be reduced mechanically, using a percutaneously placed intra-aortic balloon counterpulsation pump (IABP). IABP is most commonly used in myocardial infarction and in the immediate postoperative period following coronary artery bypass. IABP provides mechanical afterload reduction and improves coronary artery perfusion. IABP demonstrates survival benefit primarily in myocardial infarction patients who have reversible pathology and has been used successfully in high-risk patients undergoing noncardiac surgery [72].

Although afterload reduction may be beneficial in improving cardiac performance, the patient with aortic stenosis leading to shock may be harmed by use of these agents. In this disease, left ventricular wall tension remains high, and afterload reduction only serves to reduce coronary perfusion by reducing coronary perfusion pressure.

In septic and neurogenic shock, it will often be necessary to counteract the vasodilatory effects of the underlying disease process. Recent studies suggest that norepinephrine should be used as the first-line agent and vasopressin in low doses (0.01 to 0.04 U per minute) should be added when patients fail to respond to norepinephrine. Vasopressin should be used with caution in patients with poor cardiac function [2]. Studies in Europe with terlipressin, a synthetic vasopressin analogue with theoretical advantages over arginine vasopressin, are ongoing [73].

Oxygen Transport

The goal of shock resuscitation is to improve tissue oxygenation so that oxygen delivery meets the demand of cells to function aerobically. Beginning in 1977, Shoemaker et al. suggested in a series of clinical trials that resuscitation to achieve "supranormal" CI (> 4.5 L per minute per m^2), DO_2I (> 600 mL per minute per m^2), and $\dot{V}O_2I$ (> 170 mL per minute per m^2) levels was associated with improved high-risk patient survival following operative procedures [74,75]. Subsequent trials, however, identified that it is a patient's ability to spontaneously reach such supranormal levels of oxygen transport that is predictive of survival and not the applied intervention itself [74–79]. In fact, Balogh et al. have demonstrated that supranormal resuscitation is associated with a higher incidence of over-resuscitation, intestinal malperfusion, abdominal compartment syndrome, multiple system organ failure, and death [80]. They concluded that traumatic shock patients should be resuscitated to achieve a DO_2I of 500 mL per minute per m^2 during the first 24 hours of resuscitation and that maintaining such a level beyond 24 hours is rarely beneficial unless evidence of ongoing shock is present. The potential benefits of adequate sedation and analgesia as a method to reduce oxygen demand must always be considered in any patient who presents with shock.

SYSTEMATIC APPROACH TO THE TREATMENT OF SHOCK

Perhaps most noteworthy in the recent literature on the treatment of shock are multiple studies demonstrating that a proactive, systematic, evidence-based approach to shock resuscitation improves patient outcome (Table 157.4) [1–3]. The Surviving Sepsis Campaign is a multimodality approach to timely resuscitation of the septic patient encompassing diagnosis, source control, fluid resuscitation, vasoactive medications, appropriate antimicrobial therapy, correction of oxygen transport inequalities, low-dose steroid administration for relative adrenal insufficiency, selective use of recombinant human activated protein C, targeted blood product administration, mechanical ventilation strategies geared at reducing barotrauma, sedation, and neuromuscular blocking protocols that include daily interruption, glycemic control, deep venous thrombosis prophylaxis, and stress ulcer prophylaxis [2,3]. This comprehensive approach to the critically ill patient has also been applied with marked success outside the ICU setting using the "rapid response team" concept to treat nonseptic shock patients as well [81]. Many of these same tenets of shock resuscitation are also applicable to the other shock states that may be encountered.

Shock resuscitation continues to evolve as new research identifies the pathophysiology of the various shock states. Numerous treatments for shock are currently being evaluated

TABLE 157.4

SUMMARY OF ADVANCES IN MANAGING SHOCK BASED ON RANDOMIZED CONTROLLED CLINICAL TRIALS

- Patients with hypotension or evidence of anaerobic metabolism should receive immediate early goal-directed resuscitation to restore systemic perfusion and oxygenation within six hours [1,2]
- Fluid resuscitation using either 0.9% normal saline or 4% albumin may be considered equivalent with similar outcomes in 28-day mortality [64].
- Patients in shock should be resuscitated to maintain a mean arterial pressure ≥ 65 mm Hg [2,3]
- Centrally administered norepinephrine or dopamine should be considered the vasopressors of choice for noncardiogenic shock resuscitation [2]
- Dobutamine is the inotropic agent of choice for cardiogenic shock [2]
- Low-dose dopamine infusions should not be used for renal protection [69]
- Resuscitation to achieve supranormal levels of oxygen delivery or consumption do not improve patient outcome [78,80]
- Recombinant human activated Protein C should not be administered to septic patients with an APACHE-II < 25 [2]
- Corticosteroids should not be used to treat septic shock unless the patient demonstrates evidence of symptomatic adrenal insufficiency [2]
- Transfuse packed red blood cells when hemoglobin decreases to < 7.0 gm/dL. A higher hemoglobin level is appropriate in patients with myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, lactic acidosis, or closed head injury [2,54].
- A 1:1:1 red blood cell/plasma/platelet transfusion strategy should be utilized in patients with massive hemorrhagic shock (≥ 4 units of packed red blood cells over 1 h or ≥ 10 units over 24 h [more than one total blood volume]) [67].
- Hypothermia should be rapidly corrected in any patient with shock [30].
- Patients resuscitated to elevated levels of preload have significantly improved visceral perfusion than those resuscitated to normal preload with additional inotropes. Elevated preload levels do not affect pulmonary function [49].

including nitric oxide therapy, levosimendan, intravenous immunoglobulin, continuous hemodiafiltration, factor VIIa, and statin therapy among others [82–86]. Time will determine whether these therapies provide a survival benefit to the patient with shock.

SUMMARY

Shock is a common and highly lethal condition that is commonly encountered in the critically ill patient. Its cause is varied and complex. It may present in a spectrum from subclinical laboratory abnormalities to complete cardiovascular collapse. A high degree of clinical suspicion and thorough evaluation are essential to both making the diagnosis and initiating timely resuscitative therapy. Inadequate tissue perfusion that is unresponsive to initial treatment should lead to early, goal-directed therapy. Correction of abnormalities in ventricular preload, contractility, afterload, and oxygen transport are the first steps to breaking the cycle of cellular injury and microcirculatory failure. Correction of the precipitating, underlying condition is essential for patient survival. Early treatment to predefined physiologic endpoints reduces the potentially devastating complication of end-organ dysfunction and failure.

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CHAPTER 158 ■ RESUSCITATION FROM SHOCK FOLLOWING INJURY

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After the initial evaluation and operative management of the surgical/trauma patient, many patients require further resuscitation, support, and care in an intensive care unit (ICU) setting. This chapter provides a brief outline of considerations, priorities, treatment algorithms, and the newest innovations that may assist any intensivist tasked with managing such critically ill surgical patients.

STATEMENT OF THE PROBLEM

Surgical patients die from shock abruptly through lack of oxygen delivery to the heart and brain, or subacutely through development of multiple organ dysfunction from late recognition of shock or inadequate resuscitation. Unlike the typical nonsurgical critically ill patient, exsanguination is often the cause of death in the surgical/trauma patient, second only to central nervous system injuries as the cause of death of trauma victims in the United States [1–3]. The control of hemorrhage has been identified as a priority in modern trauma patient care, second in importance only to adequate ventilation [4]. Advanced Trauma Life Support teaches a schema that incorporates the vital signs, skin color, capillary refill, and mentation to alert the physician to how severely injured the patient may be and help to quantify how much blood the patient may have lost [4]. By the time the blood pressure falls, the patient has lost 30% to 40% of his or her blood volume, or approximately 2,000 mL. This situation demands rapid action, but action should not wait until this point has been reached.

One classification system defines four types of shock: *Hypovolemic* (such as dehydration, diarrhea, and hemorrhage, the most common form of shock following major trauma), *distributive* (such as septic shock, the most common form of shock in the late phase of recovery—5 days or more—after major surgery/trauma), *cardiogenic* (such as from massive myocardial infarction or arrhythmia), and *obstructive* (such as from tension pneumothorax, pulmonary embolus, or pericardial tamponade). By far, hemorrhagic shock is the most common form following major surgery/trauma and the major focus of this chapter (although the astute physician should always keep tension pneumothorax in the differential diagnosis). Therefore, in most instances, the ICU physician faced with a surgical patient in shock should direct initial efforts toward correction of hypovolemia.

Without obvious external bleeding, vital signs and evidence of organ hypoperfusion are assessed to evaluate the patient for significant or ongoing hemorrhage. A falling hematocrit may be a sign, but as hemorrhage causes loss of cells and fluid in equal proportion, an isolated normal hematocrit should not be reassuring to the clinician. With very rapid hemorrhage, a patient can die with a normal hematocrit. A fall in central venous oxygen saturation when the cardiac output remains the same may be one of the earliest signs of hemorrhage in the ICU setting as the body begins to extract more oxygen from the remaining blood.

PHYSIOLOGY OF EFFECTS OF HEMORRHAGE

The physiologic responses to hemorrhage can be broken into three categories: Hemostasis, oxygen delivery, and immunology.

Hemostasis

If bleeding does not stop, then no intervention can prevent death. It is this concept that has led to some of the most heated debates in the resuscitation literature: "Does resuscitation promote tissue perfusion and cellular metabolism, thus increasing survival, or does the increase in blood pressure destroy clot, promote rebleeding, and decrease survival?" [5]. The astute physician recognizes that both concepts are true. Cellular metabolism must be ensured, without overwhelming the clotting mechanism.

After injury, the body attempts to stop hemorrhage by clotting at the site of vascular injury. This is accomplished by the interaction of circulating clotting factors, platelets, and tissue factors from the injured cells. These factors work primarily to form a "plug" initiated by the physical presence of the platelets and augmented by the cross-linking of fibrin to form a more permanent seal. The tissue injury factors released may also lead to constriction of the local blood vessels to decrease the blood flow to the leaking area concurrently with platelet plug formation and is mediated both locally by tissue factors as well as centrally. Finally, when the blood loss leads to a fall in the blood pressure, the clotting efforts are aided by a smaller vessel diameter, decreased wall tension, and lower pressure head.

Oxygen Delivery

In 1872, Gross called shock a "rude unhinging of the machinery of life." Although this definition is accurate, it is not precise. It is at the level of cellular oxygen delivery and utilization that the understanding of shock is defined. Without oxygen, the cells may survive briefly using anaerobic metabolism. Many of the physiologic defense mechanisms work to augment this delivery and depend on oxygen-carrying capacity, cardiac output, and oxygen delivery to and utilization by the cell.

The oxygen-carrying capacity of blood depends on the amount of circulating hemoglobin, which diminishes continually during hemorrhage. Although erythropoietin stimulates the production of new red blood cells (RBCs) and eventually restores hemoglobin over weeks, this response does not acutely restore oxygen-carrying capacity [6]. As hemorrhage proceeds, the body becomes incapable of supporting metabolic need. The primary defense, however, is the extra capacity inherent in the human system: only approximately 25% to 30% of the transported oxygen is normally used, leaving central venous or mixed venous oxygen saturations in the range of 70%. When fully stressed, extraction improves as anaerobic metabolism leads to lactic acidosis, which shifts the oxygen dissociation curve to favor release of oxygen at the tissue level. This allows much more oxygen to be removed from the hemoglobin, and much lower central venous oxygen saturations.

Cardiac output is the product of heart rate and stroke volume. There is reserve built into the heart rate, in that most people use only approximately two-thirds of their maximal heart rate. Pain, fear, and a variety of baroreceptors release catecholamines and other factors in response to hemorrhage. These lead to an increased heart rate, and thus increased cardiac output and oxygen delivery. With a few exceptions, in the elderly or those with heart disease, this response is maximally achieved by the body, in an unaided fashion.

The stroke volume can be increased by increased contractility through the direct effects of many of the same substances that increase heart rate. In hemorrhage, however, the primary component of cardiac output is the volume of blood coming into the heart (preload). During hemorrhage, the preload falls. As the blood pressure falls, oncotic forces predominate and fluid begins to shift into the vascular space. This "borrowing" of fluid from the interstitial, and ultimately from the intracellular, space is gradual, with a gradual restoration of the blood pressure—often not to normal—which allows time for the clotting mechanisms to stop the bleeding and stabilize the clot.

Other factors that restore the preload include the prevention of further fluid loss via the kidney. A lower blood pressure leads to less filtration and less fluid removed in urine. In addition, antidiuretic hormone and the renin–angiotensin systems act to augment this response. Catecholamines and large proteins circulate as part of the defense signaling systems. These augment the oncotic pull. The glucose that increases with the release of corticosteroids also acts to pull fluid into the vascular space. Finally, the body is willing to shunt blood away from most areas of the body to support cardiac preload and the brain. This shunting is very evident in the pale clammy skin of hemorrhagic shock. Initially it is less evident in the relative ischemia that occurs in every other organ of the body.

Oxygen delivery (DO_2) to the tissues includes the variables of cardiac output, arterial oxygen content (CaO_2, the total amount of oxygen in the blood), which includes the amount of hemoglobin that is present. During hemorrhage, these components are altered, and oxygen delivery may be decreased. Cardiac output can be indexed to body surface area and expressed as cardiac index, which when multiplied by CaO_2 yields an oxygen delivery index (DO_{2I}). Normal DO_{2I} is roughly 450 mL per minute per m^2 and it may increase by as much as 30% in response to injury. The primary goal of shock resuscitation is the early establishment of "adequate" oxygen delivery (DO_2) to vital organs; however, adequate is subject to ongoing debate.

The complications of a "successful" resuscitation that should be watched for are related to ischemia and reperfusion injury. These may manifest as multiple organ dysfunction syndrome or individual organ dysfunction. Hepatic dysfunction

may present as jaundice and coagulopathy. Pulmonary dysfunction and acute respiratory distress syndrome may be seen as renal failure, with rising blood urea nitrogen and creatinine. Compromise of intestinal mucosa may lead to sepsis, bleeding, or perforation.

Immunology

Hemorrhagic shock alone, without tissue injury, was once thought to have minimal consequences [7]. Hemorrhagic shock alone has been shown to result in a multitude of responses, however, especially in the immune system. The immune system is intended to protect the body from infectious invaders and remove aberrant cells to prevent cancer. During shock, cells produce messengers or mediators that signal for the help of this system [8]. During reperfusion, these mediators are released widely into the systemic circulation.

Currently, a focus in hemorrhagic shock research is the effect of resuscitation on the immune and coagulation system. Extensive research in the last decade has shown that hemorrhagic shock from trauma activates both the inflammatory and coagulation system, resulting in profound perturbations in both. This is often manifested by a spectrum of clinical problems starting from acute lung injury, progressing to acute respiratory distress syndrome, systemic inflammatory response syndrome, hypo- or hypercoagulation, bleeding or diffuse thrombosis, and even multiple organ dysfunction syndrome [9]. One of the major areas of study involves the activated immune response that results in enhanced activation and increased adhesion of leukocytes. During this activated stage, neutrophils can release harmful reactive oxygen species, which are thought to play a major role in loss of capillary integrity. This leads to edema and the sequestration of fluid in the tissues outside the vascular space.

Although it has been clear that the immune response occurs in response to shock and reperfusion, it now seems that some of the resuscitation fluids used to treat the shock may trigger this altered immune and coagulation response. The immunologic response to various resuscitation fluids is now an area of intense research [10,11].

HEMORRHAGIC SHOCK MANAGEMENT

The first goal in hemorrhagic shock, following assessment of the ABCs (airway, breathing, and circulation), is to stop ongoing bleeding. In the surgical/trauma patient reaching the ICU, this has generally been accomplished in the emergency department (ED), interventional suite, and/or operating room. During the ICU phase, resuscitation is continued, and can last 24 to 48 hours. The goal of resuscitation is to restore normal perfusion to all body organ systems, using the components of oxygen delivery: hemoglobin, cardiac output, and oxygenation. In hemorrhagic shock, this primarily involves hemorrhage control, reversal of coagulopathy, and then administration of sufficient volumes of blood products and crystalloid fluid volume to restore normal aerobic metabolism.

Confirmation of a hypoperfusion state (shock) is obtained through simple examination and a single blood test. Shock is diagnosed by the effect of hypoperfusion on the body's organ systems: low blood pressure, tachycardia, oliguria, tachypnea, decreased mental status or agitation, skin cyanosis, pallor, decreased pulse character, or mottling. Equivocal cases can be confirmed by obtaining an arterial blood gas and looking for a base deficit exceeding 6 or a serum lactate assay (more than 2 mmol per L). Hypoperfusion implies inadequate delivery of oxygen to the body's cells. Oxygen delivery is a function of cardiac performance, arterial hemoglobin content, and arterial oxygen saturation. All attempts to correct shock involve optimizing these three variables. Hypotension is not synonymous with shock, which can be present in a normotensive patient. Conversely, not all hypotensive patients are in shock. Hypotension, like many other physical findings, is but one sign helpful in the overall clinical picture of shock diagnosis. As detailed below, reestablishment of normal heart rate, blood pressure and urine output does not equate to resolution of shock; resolution of tissue hypoperfusion as manifested by lactate clearance does.

Resuscitation of the patient in shock should be approached in two phases, based on the end points of the resuscitative effort. In the first phase, the patient should be resuscitated to a systolic blood pressure of 80 to 100 mm Hg or mean arterial pressure of 55 to 65 mm Hg, a urine output of 0.5 mL per kg per hour, and an arterial oxygen saturation of 93% or higher. These end points are pursued to prevent imminent death from hypoperfusion to the heart and brain, and should be achieved optimally within 1 hour.

In the second phase, resuscitation is continued with fluid, as well as inotropic and vasopressor agents, as needed, to the goal of eliminating the base deficit of metabolic acidosis, or, if available, restoring the serum lactate or base deficit to a normal level. This end point is important in reversing systemic anaerobic metabolism, which, if unrelieved, leads inexorably to multiple organ failure (MOF). This goal should be accomplished within 12 to 24 hours.

Lessons Learned from War

The modern-day trauma system owes a large debt to combat casualty care. Techniques from system development to operating room procedures have their roots in battlefield medicine. Resuscitation as well, is no stranger to advancement during wartime. To understand the advancements made and differences that exist with modern combat resuscitation strategies it is important to understand the history of combat resuscitation.

A modern ATLS resuscitation strategy of 2 L of crystalloid owes its roots to strategies developed during the Vietnam War. Based on research by Shires [12,13], Dillon [14], and others, the need for volume resuscitation was brought to the forefront to replace an interstitial volume debt secondary to intravascular movement in hemorrhagic shock. High volume crystalloid resuscitation strategies were used to replace volume loss encountered by the bleeding soldier in ratios of 3:1 to as high as 8:1. The physiology was sound, but disappointingly when outcomes were examined, clinical efficacy in the way of improved survival was not seen over previous war efforts with Killed in Action rates of 16% for the US Civil War, 19.6% for World War I, 19.8% for World War II, and 20.2% for the Vietnam War [15]. In fact, the adopted strategy of IV fluid administration would spawn its own set of complications, most notably the emergence of Da Nang lung known more widely now as acute respiratory distress syndrome. Initially felt to be the result of the volume of resuscitation, eventually its mechanisms linked to immunologic effects would come to be understood by Ashbaugh et al. in their case series of 12 patients (seven with trauma) published in the Lancet in 1967 [16].

High-volume crystalloid resuscitation strategies were further supported by Shoemakers early prospective study of 67 patients with greater than 2,000 mL of blood loss. Supranormal endpoints of resuscitation, defined as a cardiac index >4.52 L per minute per m^2, oxygen delivery ≥ 670 mL per minute per m^2, and oxygen consumption ≥ 166 mL per minute per m^2 were assessed against "standard" therapy. Survival was nearly double in the supranormal group as well as statistically significant decreases in length of ICU stay, mean number of organ

failures, and days of ventilation [17]. Despite these promising results, several other groups failed to achieve similar findings. More importantly with an ever increasing understanding of the immunology of intravenous fluids and resulting proinflammatory properties the complications of high-volume crystalloid resuscitation for combat casualties came into question.

If aggressive crystalloid resuscitation was not the answer, then what would the optimal resuscitation strategy be? A report by the Institute of Medicine in 1999 as well as two consensus conferences held by Office of Naval Research, the US Army Medical Research and Material Command and the Uniformed Services University of Health Sciences in 2001 and 2002 tried to answer the question.

The IOM report was the first to recognize the several inadequacies of the then standard fluid therapy. First noted was the paucity of good Level I and II data to support the then standard of care. Second, the immunologic activity of common intravenous fluids used and deleterious effects of high-volume resuscitation was better defined as it related to complications [17]. This report would mark a significant paradigm shift. Initial recommendations were to remove the racemic mixture of D and L Lactated Ringers (still clinically available) in favor of L-isomer only. Replacement of lactate with ketones was advocated. Finally, the report supported the initial battlefield use of low volume hypertonic saline (HTS) resuscitation [18]. A 250-mL bolus of HTS was chosen based on research showing decreased neutrophil activation as well as increased oncotic properties as well as the battlefield logistics of less fluid to carry for frontline medics.

The 2001 consensus conference took it one step further by defining what the endpoints of resuscitation would be on the battlefield [19]. Triggers for fluid resuscitation would be systolic blood pressure less than 80 mm Hg or absence of palpable radial pulse, decreasing blood pressure, or altered mental status with no confounding brain injury [19]. This protocol allowed for "permissive hypotension" during resuscitation until definitive hemorrhage control. The goal was not to return blood pressure to normal, but rather to target clinical goals of mentation and palpable pulse. These protocols were developed with several civilian trauma studies in mind.

The first by Bickel and Mattox done at the Ben Taub in which 598 adult patients sustaining penetrating torso trauma with a systolic blood pressure less than 90 were assigned to either standard fluid therapy with Lactated Ringers or IV cannulation with no fluid infusion. Although controversies with study design and protocol surround the results, a significant survival benefit 70% versus 62% was seen for the delayed resuscitation arm [20].

Second were several studies that suggested early aggressive fluid resuscitation before hemorrhage control may have a deleterious effect. As early as 1964, Shaftan et al. published data showing the effects of aggressive volume correction slowed spontaneous control of arterial bleeding [21]. This was followed by military research data done in swine by Bickell et al. Adult swine had their infrarenal aorta cannulated with a stainless steel wire. The wire was pulled creating a 5-mm aortotomy and free intraperitoneal hemorrhage. Eight pigs received 80 mL per kg of Lactated Ringers where the control group received nothing. Hemorrhage was significantly higher in the intravenous fluid group (2,142 ± 178 mL vs. 783 ± 85 mL, $p < 0.05$) as well as mortality (8 of 8 vs. 0 of 8, $p < 0.05$) [22]. This ultimately culminated in a complete 180-degree shift from the high volume crystalloid resuscitation seen in the Vietnam War.

If awake, alert, and having a palpable pulse, a soldier sustaining a penetrating wound should have an IV placed, but no fluids would be infused. PO fluids would be encouraged and evacuation undertaken to the next level of care. If resuscitation had to be undertaken, again recognizing a low-volume strategy the recommendation of the panel was for 500 mL hetastarch (Hespan or Hextend) as FDA approval for HTS was lacking. The hetastarch bolus could be repeated at which point a reassessment was done and if no response the possibility of futility was entertained [23].

Expanding on this the 2002 consensus conference held in conjunction with the Canadian Defense and Civil Institute for Environmental Medicine reexamined prehospital requirements for fluid therapy. The "hypotensive" strategy was again approved, but the recommendation for initial battlefield fluid was changed to hypertonic saline dextran (HTS-D) based on then current research showing a favorable volume expansion profile of the dextran with the inflammatory inhibition of the HTS component [24,25].

Current strategies in the Iraq and Afghanistan wars are very similar. First and foremost, the problem had to be defined with the unique set of circumstances that are present in live fire situations. The first point of care would be the battlefield medic. It was recognized that logistical problems exist in bringing care to the wounded at the point of injury. Hemorrhage control still remains the first priority in resuscitating the injured patient, for if quick, effective hemostasis cannot be achieved fluid therapy has no hope of working in austere environments where definitive therapy may be hours away [23]. This has led to the reintroduction of vascular tourniquets, the use of Battlefield hemostatic dressings, and newer therapies such as Factor VII to arrest hemorrhage so that resuscitation efforts can be effective, a discussion of which is beyond the scope of this chapter.

As recognized in the previous consensus conferences, if medics are to be mobile and effective on the battlefield they need the ability to carry their supplies with them [18,19,23,24]. This makes low-volume intravascular expansion much more attractive. For this reason, colloid solutions, specifically Hespan or Hextend, continue to be the fluid of choice for military applications [23]. HTS-D has fallen out of favor due to more current civilian prehospital data that has shown an increase in mortality in trauma patients during interim analysis of the recent ROC trial [26].

With the choice of fluids now made (Hespan or Hextend), the next decision point is how to get those fluids into an injured soldier. Trauma providers know the key tenet of ATLS "two large-bore IVs in the antecubital fossa." This principle becomes increasingly difficult in combat conditions. To this end, the US military takes a different approach. If awake, alert and having a palpable radial pulse, a wounded soldier with a palpable radial pulse have a single 18-gauge peripheral IV placed (chosen for ease of cannulation versus a larger bore IV) and PO fluids encouraged [23]. If IV access cannot be obtained or conditions will not allow access, a sternal intraosseous device is placed. Sternum was chosen as the reproducible target as extremity injuries prevail in current warfare and the trunk remains relatively protected with modern armor. The sternal IO can be placed with reproducible landmarks quickly and in low- or no-light conditions making it extremely beneficial in modern combat [23].

Resuscitation then continues as appropriate with evacuation to the next level of care. It is at this level that the paradigm has shifted dramatically. The emphasis now is on damage control. This pertains not only to the way in which the operations are done (quick procedures leaving abdominal wounds open, temporary packing for hemorrhage control, and temporary vascular shunts) but also to the way in which resuscitation is continued. The use of early blood and coagulation component therapy as well as fresh whole blood (FWB) is emphasized. Again logistics dictate limited storage capabilities in far forward treatment centers. This continues to promote a walking blood bank using fellow combat troops as donors, a luxury not afforded by the civilian trauma provider.

Clinically, FWB has been demonstrated to reverse dilutional coagulopathy, with evidence that a single unit of FWB has a

hemostatic effect similar to 10 units of platelets [27–34]. In a retrospective study of the results of the FWB procedures for one U.S. Combat Support Hospital in 2004, 87 patients received 545 units. In that experience the FWB drive was called for only after the patient had received a massive transfusion, yet the transfusion of FWB resulted in significant improvements in both hemoglobin concentration and coagulation parameters [32].

The nature of military medical logistics frequently limits the availability of FFP, platelets, and cryoprecipitate for transfusion in theaters, giving the battlefield physician few options in the treatment of traumatic coagulopathy. However, the use of FWB in massively transfused patients may circumvent the problem of dilutional coagulopathy. Consider the usual mixture of one packed RBC unit (335 mL) with a hematocrit of 55%, one unit of platelet concentrate (50 mL) with 5.5×10^{10} platelets, and one unit of FFP (275 mL) with 80% coagulation factor activity. This combination results in 660 mL of fluid with a hematocrit of 29%, 88,000 platelets per μL, and 65% coagulation factor activity. By definition, transfusion of these standard components will only serve to further dilute critical factors in a bleeding casualty. In contrast, FWB is replete with functional platelets as well as fully functional clotting factors. A 500-mL unit of FWB has a hematocrit of 38% to 50%, 150,000 to 400,000 platelets per μL, and 100% activity of clotting factors diluted only by the 70 mL of anticoagulant [35]. In addition, the viability and flow characteristics of fresh RBC are better than their stored counterparts that have undergone metabolic depletion and membrane loss.

Initial retrospective studies by Holcomb found higher 24-hour (96% vs. 88%, $p = 0.018$) and 30-day (95% vs. 82%, $p = 0.020$) survival in a group of combat casualties when FWB was used [36]. The immunology and pathophysiology of improved clinical outcomes continues to be an active area of research. Also reported from military and civilian evidence is that higher ratio FFP to PRBC improves outcomes [37–39]. The exact ratio is still part of ongoing research, with some evidence suggesting that there may be a survival bias in those patients receiving higher ratios. Despite these controversies, the early and aggressive use of blood and coagulation factors forms the cornerstone of damage control resuscitation.

DAMAGE CONTROL RESUSCITATION

The concept of damage control resuscitation or hemostatic resuscitation has rapidly evolved on the modern battlefield. This concept is philosophically derived from the widely practiced damage control surgery approach to severely injured patients. Understanding the epidemiology of combat casualties is paramount to devising a logical resuscitation strategy. Most deaths (80%) in combat operations are not preventable [40,41]. Of the remaining 20% of potentially preventable deaths in combat casualties, two-thirds are from hemorrhage. Furthermore, the killed in action rate is lower than at any time in history, while the died of wounds rate has increased, largely due to improved body armor, rapid evacuation, improved extremity hemorrhage control, and medic training [40]. With the recent widespread use of tourniquets and hemostatic dressings for compressible hemorrhage control, the current unmet need is for rapid, effective interventions for noncompressible hemorrhage from the neck, axilla, thorax, abdomen, groin, and pelvis.

Fortunately, most casualties receive at most one to four units of packed RBCs after injury and are not at high risk of presenting or developing a coagulopathy and subsequently dying [42]. Only 5% to 10% of all combat casualties require massive transfusion (10 or more units of packed RBCs) and this group constitutes those at risk for hemorrhagic death [43]. These same patients are those who will benefit from early use of recombinant activated factor VII (rFVIIa), as described in the Clinical Practice Guideline (Table 158.1).

The 5% to 10% of all combat casualties that require massive transfusion fall into two broad categories. Group 1 patients are the wounded who are clearly in profound shock, arrive moribund, and are resuscitated with heroic efforts. These casualties do not pose a diagnostic dilemma; rather, they require immediate hemorrhage control and very rapid resuscitation with the optimal ratio of all available products. Surgically, the only question is what cavity to enter first, as they usually have multiple significant injuries. Frequently, these casualties have severely injured extremities, requiring life-saving tourniquets and delayed completion amputations after successful truncal hemorrhage control. These casualties, if surviving the initial 10 to 15 minutes resuscitation in the ED, require the full massive transfusion protocol and surgical intervention described in the following sections.

Group 2 patients are more difficult to recognize. They are typically the young soldier with incredible physiologic reserve who arrive "talking and looking good," who are actually in shock, have had significant blood loss, and soon progress to cardiovascular collapse. This classic presentation occurs once a week at a busy combat hospital. The challenge is rapidly separating these critical casualties from those who are really hemodynamically stable. These casualties require rapid and accurate diagnosis of their hemorrhagic injury. This group needs immediate hemorrhage control, as fast as group 1; however, they are much more difficult to initially diagnose. Traditional reliance on mental status, blood pressure and pulse rate is notoriously inaccurate for individual risk stratification [44–47].

Fortunately, there are five risk factors that are easily identified very early in the hospital course of severely injured casualties, each of which independently predicts the need for massive transfusion and/or increased risk of death. These simple variables are now available within 2 to 5 minutes after presentation in every ED and each of these variables is independently associated with massive transfusion or death after trauma; any one of them should prompt activation of the massive transfusion protocol (discussed later).

First, an initial international normalized ratio (INR) of 1.5 or more reliably predicts those military casualties who will require massive transfusion [48–50] Patients who have a significant injury present with a coagulopathy as a marker of severe injury. Severity of injury and mortality is linearly associated with the degree of the initial coagulopathy [35,47–50]. Second, a base deficit of 6 or more is strongly associated with the need for massive transfusion and mortality in both civilian and military trauma. Patients have an elevated base deficit before their blood pressure drops to classic "hypotension" levels [51–53]. Third, a temperature of 96°F or less is associated with an increase in mortality. Trauma patients who are hypothermic are in shock, not perfusing their mitochondria, and are not generating heat fast enough to keep up with their ongoing heat loss [52–54]

Fourth, a hemoglobin of 11 mg per dL or less on presentation to the ED is associated with massive transfusion and a mortality rate of 39% [43]. Otherwise, young healthy soldiers who present with a low hemoglobin have only one reason for their anemia, namely, acute blood loss [43,55]. Lastly, a systolic blood pressure of 90 mm Hg or less is indicative casualties who have lost more than 40% of their blood volume (2,000 mL in an adult), are experiencing impending cardiovascular collapse, and have a significantly increased mortality [56,57].

The current resuscitation protocol for combat casualties not only has an affect on current military outcomes (initial reports show Case Fatality Rates dropping from a historic 20% to close to 10%), but has provided exciting tools for civilian trauma providers [40,58].

TABLE 158.1

U.S. CENTRAL COMMAND CLINICAL PRACTICE GUIDELINE FOR USE OF RECOMBINANT FACTOR VIIA (RFVIIA) AND THAWED PLASMA

1. Background: The most critically injured casualties present hypothermic (T ≤ 96°F) acidemic (BD ≤ 6), with a coagulopathy (INR ≥ 1.5), hypotensive (SBP ≤ 90 mm Hg) or with a Hgb ≤ 11). Interventions aimed at reversing the coagulopathy starting as soon after arrival as possible may improve survival.
2. Recombinant factor VIIa is FDA-approved for use during critical bleeding or surgery in hemophilic patients with inhibitors to factor VIII or IX. rFVIIa has been shown to be safe and decreases transfusion requirements in humans with life-threatening hemorrhage, including patients with hypothermia (30°C–33°C, pH > 7.1). In a total of seven prospective randomized surgical trials, the drug causes no increase in any complication.
3. Plasma used in a 1:1 ratio with PRBCs has been shown to improve survival in combat casualties.
4. In the combat surgical setting, rFVIIa and plasma should be used in patients who are
   (a) Hypotensive from blood loss (SBP ≤ 90 mm Hg)
   (b) Have a base deficit ≥ 6
   (c) Hypothermic (*T* ≤ 96°F)
   (d) Coagulopathic (clinically or an INR ≥ 1.5)
   (e) Have a Hgb ≤ 11
   (f) Have weak or absent radial pulse character
   (g) Have more than one major amputation
   (h) Have major truncal injury with a positive FAST examination
   (i) Abnormal mental status from trauma or CT scan with intracranial injury
   (j) Have > 1,000 mL immediately out of a chest tube or > 200 mL/h
   (k) Anticipated and actual transfusion of > four units of PRBCs
   (l) Require damage control maneuvers
   (m) Require fresh whole blood
5. Guidelines for administration
   (a) Protocol for use
      (i) Infuse rFVIIa at dose of three vials (2.4 mg) or 90–120 μg/kg IV push.
      (ii) If coagulopathic bleeding continues 20 min after infusion
         (1) Administer two additional units fresh whole blood or four units FFP, 10 packs of cryoprecipitate and 6 packs of platelets
         (2) Redose rFVIa 90–120 μg/kg rFVIIa IV push.
   (b) Administration limits
      (i) Four doses (typically 12 vials) within a 6-h period.
      (ii) If bleeding persists after four doses, there should be attention to conservation of resources. Consult the senior surgeon before administering more rFVIIa.

BD, base deficit; CT, computed tomography; FAST, focused abdominal sonogram for trauma; FDA, Food and Drug Administration; Hgb, hemoglobin; INR, international normalized ratio; PRBC, packed red blood cell; SBP, systolic blood pressure; T, temperature.

Emphasis on early hemorrhage control and damage control resuscitation through aggressive replacement of blood component and coagulation factors still needs further study, but remains one of the positive hallmarks of modern combat medicine. From the point of injury on the battlefield to the arrival at definitive care facilities the current combat casualty enters into a well thought out system of multiphasic resuscitation with specific goals to be achieved at each level; early hemorrhage control, limited intravascular replacement until definitive control is available, and the early use of blood and coagulation factors in a damage control resuscitative strategy.

Civilian Experience

Damage control resuscitation defines a new philosophy of acute traumatic resuscitation. Its tenants define a number of important maneuvers during the resuscitation. First is permissive relative hypotension, with a goal systolic blood pressure slightly below normal. Next is prevention and treatment of hypothermia, acidosis, and hypocalcemia, while avoiding hemodilution with crystalloid fluids. Early surgical control of bleeding is also tantamount to damage control resuscitation. Lastly, hemostatic resuscitation with blood products in high ratios of fresh frozen plasma (FFP) and platelets to packed red blood cells, with appropriate use of adjuvants like factor VIIa, and fibrinogen containing compounds, is considered fundamental to this approach to the hemorrhaging patient [59].

There has been ongoing controversy in the surgical literature concerning the optimal use of resuscitative fluids. Questions of type, amount, and timing dominate the ongoing discussion. In addition, some authors maintain that the differences between civilian and military mechanisms of injury limit the applicability of military data to the civilian practice patterns. There is some belief that combat-related injuries result in a distinct patient population, and that lessons learned there may not be translatable to the civilian population [60,61]. However, multiple civilian studies in Europe and in the United States demonstrate similar results to wartime casualties and the benefits to aggressively resuscitating these patients with plasma and platelets versus excessive crystalloid. The evidence in these studies is all retrospective, and is subject to survivor bias and multiple other confounding variables. Unfortunately, no prospective randomized trials have been conducted examining any resuscitation strategy, including damage control resuscitation.

The early coagulopathy of trauma, identified by as early as 1969 by Simmons and Borowiecki, and highlighted separately by Brohi and MacLeod is a common and dangerous condition that many patients manifest upon admission to the emergency department [50]. Brohi defines coagulopathy as prothrombin time (PT) over 18 seconds, activated partial thromboplastin time (aPTT) over 60 seconds, or thrombin time over 15 seconds. This London study found a significant coagulopathy in 24.4% of patients admitted to their ED. This coagulopathic cohort had a much greater mortality (46% vs. 10.9%, $p < 0.001$) compared with those with normal coagulation studies. Contradicting previous suspicions about the contribution of fluids to coagulopathy, Brohi found that the early coagulopathy of trauma was not linked to amount of IV fluids (crystalloid and colloid) administered [49].

Adding to this observation, Gonzalez et al. demonstrated that patients that arrived to the emergency department in a coagulopathic state (INR = 1.8 ± 0.2) and received primarily PRBCs and crystalloid fluids were persistently coagulopathic on admission to the ICU (INR = 1.6 ± 0.1). Ninety-one patients were identified who received > 10 units of PRBCs in the first 24 hours of admission. According to the massive transfusion protocol at that time, FFP was not transfused until the patients received six units of PRBCs. Once admitted to the ICU, patients received a ratio of FFP/PRBC 1:1. Using univariate logistic regression analysis, the authors concluded that risk of mortality was increased with higher initial ICU INR. This study highlighted the potential importance of earlier administration of FFP and its possible benefits in the form of improved patient survival [34].

Recent civilian studies have demonstrated benefits in survival with high FFP to PRBC ratios, as well as platelets to PRBCs. A study by Holcomb et al.included 466 massively transfused (≥ 10 units PRBCs in 24 hours). This retrospective multicenter study demonstrated that patients who received a high ratio of FFP to PRBCs (≥ 1:2) had increased survival (59.6%) compared with those who received a low ratio (< 1:2) of FFP to PRBCs (40.4%, $p = < 0.01$). This effect was also seen in patients who received a high ratio (≥ 1:2) of platelets to PRBCs. Those patients had 59.9% survival compared with those in the low (< 1:2) platelet to PRBCs group, who demonstrated only 40.1% survival at 30 days ($p = < 0.01$) [37]. Another paper with the same cohort of patients highlighted the importance of early (within 6 hours) administration of high FFP ratios. This study showed that a transfusion ratio of ≥ 1:1 FFP/PRBCs in the first 6 hours of admission decreased mortality at 6 hours (2% vs. 15.2% and 37.3% for ratios ≥ 1:1, 1:4 to 1:1, and < 1:4, $p = < 0.001$) and in hospital mortality (25% vs. 41.1% and 54.9% for the same groups, $p = < 0.04$). Patients receiving high platelet/PRBC ratios also had improved survival [62].

Another large single-center retrospective study examined 383 patients that received greater than 10 units of PRBCs in the first 24 hours of admission. This group, from Los Angeles, demonstrated survival benefit with higher ratios of FFP to PRBCs. Patients that received ≤ 1:3 FFP to RBC had 25% mortality, whereas those that received > 1:3 had 49% mortality. Further analysis demonstrated that the mean FFP/PRBC ratio for survivors was 1:2.1. Nonsurvivors received 1:3.7 FFP/PRBC ($p < 0.001$). They concluded that higher FFP/PRBC ratios improve survival, but unlike the Holcomb study, no benefit was shown when ratios were more aggressive than 1:3 [63].

Two recent studies from New Orleans also examine FFP/PRBC ratios and survival. Both are retrospective single center-studies. The first study reports that 135 patients, suffering 72% penetrating injuries, received > 10 units of PRBCs during the first 24 hours of treatment. All of these patients received surgical intervention. In this population they report a dramatic improvement in survival for patients that received > 1:2 FFP to PRBC compared with those who received 1:4, 26% versus 87.5% ($p = 0.0001$) [37]. The second study also examines patients who underwent emergency surgery for trauma and received > 10 units of PRBCs. The population of 135 patients were coagulopathic, as defined by INR > 1.2, PT > 16 seconds, and partial thromboplastin time > 50 seconds. A statistically significant improvement in survival was demonstrated in patients receiving 1:1 ratio of FFP to PRBCs compared with those who received 1:4, 28% compared with 51% ($p = 0.03$). This study also demonstrated an improvement in ICU days (10 vs. 23, $p = < 0.01$) in the 1:1 group versus 1:4 [64].

Other studies have demonstrated improved survival with aggressive use of FFP associated with massive transfusion protocols. One study, from Nashville, is a retrospective study with a historical control before implementation of a massive transfusion protocol that specified a ratio of 2:3 FFP to PRBC and 1:5 platelets to PRBCs. The study included 264 total patients, with 125 in the protocol group and 141 in the historical group. The authors demonstrated an improvement in survival from 37.6% to 56.8% ($p = 0.001$) after implementation of the protocol. The transfusion protocol cohort also protected against MOF in univariate and logistic regression analysis. The authors attribute the protection from multiorgan failure to the overall decrease in number of blood product units that patients received as a result of enrollment into the transfusion protocol [65].

Two recent European studies also demonstrate benefits to early plasma transfusion both in trauma patients and in other surgical patients. Maegele et al.demonstrate survival benefit for trauma patients at < 6 hours, 24 hours, and 30 days in groups that received high (1:1 and < 0.9) ratios of FFP/PRBC. This study included a multicenter retrospective review of 713 patients who received > 10 units PRBCs in 24 hours. Patients who received > 1:1 FFP to PRBCs had 6-hour mortality equal to 24.6%, 24-hour mortality at 32.6%, and 30-day morality at 45.5%. The mortality rates for 1:1 ratio were 9.6%, 16.7%, and 35.1% at the same time points ($p < 0.005$ for all values). However, these increases in survival came with the cost of increase septic-related complications. The incidence of multiorgan failure in the 1:1 FFP/PRBC group was the greatest at 67% [66].

A group of investigators in Denmark have assessed the principles of damage control resuscitation outside of trauma. A review of 832 surgical patients, including abdominal surgery, cardiovascular, orthopedic surgery, and trauma patients, demonstrated improved survival for patients receiving a ratio of FFP/PRBC equal to 1:1.3 compared with those who received 1:1.6. Mortality at 30 days was 20.4% for the high ratio group compared with 31.5% ($p = 0.0002$). Higher FFP/PRBC ratios did increase ICU days and hospital stay [67]. This study suggests that aggressive use of plasma may be indicated in all bleeding patients, regardless of traumatic etiology.

One recent multicenter study from the Glue grant project demonstrates a lower risk of mortality with a high FFP/PRBC ratio, but also highlights risks associated with transfusion. This study, by Sperry et al., included 415 patients and did not show a crude improvement in mortality, but did reveal a significant difference in 24-hour mortality (high FFP/PRBC 3.9% vs. low FFP/PRBC 12.8%, $p = 0.012$). Their high ratio group received ≥ 1:1.5 FFP to PRBCs. On Cox regression analysis, the group demonstrated a 52% reduced risk in mortality if patients received the higher FFP/PRBC ratio ($p = 0.002$). Although there was no increase in multiorgan failure or infection, the high FFP/PRBC group did have an increased (2×) risk of acute respiratory distress syndrome ($p = 0.004$) [68].

Watson et al. demonstrate an association between plasma and MOF in an examination of 1,175 patients in a prospective multicenter study. Using Cox proportional hazard regression, the researchers found a 2.1% increased risk of MOF with every unit of FFP transfused. The risk of ARDS increased 2.5% with

each unit of FFP. However, the group also reported that each unit of FFP decreased the risk of mortality by 2.9% [69].

Other civilian studies that do not find a survival benefit to high FFP/PRBC ratios. Kashuk et al., report a single-center retrospective study that examined 133 patients who received > 10 units of PRBCs in the first 6 hours. This study presented data that patients receiving FFP/PRBC ratios of 1:2 to 1:3 had the lowest predicted probability of mortality. However, the study did note improvement in coagulopathy with higher ratios of FFP/PRBC. However, because of small study size, this was not statistically significant. Also, of important note, the number of patients receiving FFP/PRBC at a 1:1 ratio was only 11 [61]. Another paper, from Baltimore, also fails to demonstrate a survival benefit from high (1:1) FFP/PRBC ratios. However, their massive transfusion subgroup was underpowered, at 81 patients, to demonstrate a survival benefit [60]. A previous study from the same group also highlighted the increased risk of infection and mortality associated with transfusion of PRBCs and FFP [70].

In summary, much like the recent military experience, the preponderance of civilian experience suggest that early and increased use of FFP and platelets in trauma resuscitation results in an overall reduction in early and late mortality. By decreasing early hemorrhagic death, there may be an association with increased risk of infection, ARDS, and multiorgan failure, but patients will survive to suffer these events.

RESUSCITATIVE FLUIDS

In hemorrhagic shock, the choice of intravenous fluid has been long debated and is beyond the scope of this chapter. Historically, a crystalloid solution such as normal saline or lactated Ringer's solution was used in the initial resuscitation. Recent evidence suggests that a more aggressive use of blood and blood products, a so-called damage control resuscitation encompassing "hemostatic resuscitation" may be more beneficial (see Damage Control Resuscitation section). Traditional regimens call for using crystalloids while awaiting blood products from the blood bank, with a rate of infusion of 500 mL to 1,000 mL bolus during 15 to 20 minutes and repeated as necessary. Certainly by the time 2 L of crystalloid have been used for resuscitation, blood product replacement should be given at similar rates of infusion. All fluids should be infused via a warming device to alleviate or prevent hypothermia. Unfortunately, this approach may worsen the coagulopathy present in the most severely injured trauma patients.

Our current recommendations are to minimize the amount of crystalloid a patient receives. Physicians in the ED have little control over what fluids a patient may receive before arrival to the hospital. Blood is the fluid of choice to resuscitate the surgical patient from hemorrhage. Although hemorrhage as the cause of shock had been debated for many years, the treatment of hemorrhage by returning blood to the body seemed logical. The first successful animal transfusion was by Richard Lower in 1665. In 1667, he transfused the blood of a lamb into a human to treat melancholy [71]. Because of transfusion reactions, blood transfusions were infrequently used before the 1900s. During this period, however, the use of autotransfusion emerged. The first American use of autotransfusion was in 1916 after a splenectomy. World War I saw the widespread use of blood banks. Brown, in 1931, was the first to autotransfuse the blood obtained from a hemothorax [72]. World War II demonstrated that truly massive use of blood across multiple theaters of war was possible. With the advent of cardiac surgery in the 1950s, autotransfusion became more common [73]. Its usefulness for the trauma victim was firmly established in the late 1960s and the early 1970s [74–78]. Complications from autotransfusion such as thrombocytopenia, disseminated intravascular coagulopathy (DIC), hypofibrinogenemia, infection, and air embolism have been well documented [78]. Improvement of delivery systems with filters and air monitors, as well as a limit to the amount of blood autotransfused, has kept these problems to a minimum. Because autotransfusion has restrictions on its use, autotransfusion alone will never be adequate for resuscitation, but the value of its use should not be overlooked.

Whole blood contains all of the factors lost by the bleeding patient; this includes plasma proteins, clotting factors, platelets, and white blood cells, as well as erythrocytes. Although FWB is a superb resuscitation fluid, it has a short storage life [36]. Infectious disease testing and blood banking inventory management issues have made FWB largely unavailable in civilian trauma centers. However, whole blood is used in many centers and clinical studies on whole blood are planned for civilian trauma patients. Prospective data collected in these studies may present an impetus for change in blood banking and provide access to this resuscitative fluid.

Usually, oxygen-carrying capacity is gained by giving RBCs. These should be typed and cross-matched to the patient to avoid transfusion reactions. In severe hemorrhage, time may not be available for cross-matching, so type-specific or even O-negative blood should be administered. PRBCs can be stored for 42 days according to current FDA standards. However, detrimental effects of stored PRBCs can be related to their age. Hyperkalemia is a well-known problem with red cell storage. Potassium is lost into the PRBC supernatant at a rate of 1 mEq a day [79]. Cardiac events have been attributed to PRBCs stored for less than a week [80]. Also multiple studies have documented increased infection risk, multiorgan failure and decreased survival associated with older RBCs [81–85]. Despite safeguards, clerical errors lead to mismatched blood administrations, with a rate of fatal major ABO blood group reactions of between 1 in 500,000 and 1 in 2 million. Currently, the risk of infection from a transfused unit is 1 in 30,000 to 1 in 150,000 for hepatitis C, and 1 in 200,000 to 1 in 2,000,000 for human immunodeficiency virus [86].

Thawed plasma is FFP that is stored for up to 5 days at 1°C to 6°C. This storage timeline is based on similar red blood cell storage guidelines and preservation of factors V and VIII, however clinical data is lacking [59,87]. It is unknown what the biologic effect is of storing thousands of proteins at 4°C for 5 days and then administrating them to patients who are in shock. As more centers are using earlier and increased amounts of plasma, thawed plasma is now routinely available at many trauma centers, and increasingly stored in emergency departments. Type AB plasma, the universal donor for plasma, is chosen initially before cross-matched product is available. Having thawed plasma available in the ED allows for identification of severely injured patients requiring massive transfusion and initiation of a protocol driven high ratio of FFP to PRBCs. Primary risks associated with plasma are transfusion-related lung injury (TRALI), infection, and multiorgan failure [69,70]. As described earlier, the risk of infection and MOF was increased 2.1% with each unit of plasma [69]. However, these observations have been made in the context of higher survival in patients that received high ratios of FFP, suggesting that those patients survived with the potential cost of developing sepsis and multiorgan failure.

Platelets are transfused in two different formulations. Pooled whole blood-derived platelets are generally transfused in six unit increments from five to six different blood donors. Apheresis platelet units are derived from a single donor and are transfused in volumes approximately equal to five to six units of pooled whole blood-derived platelets. Both types of platelets are stored at room temperature for up to 5 days. Bacterial contamination from skin flora remains the greatest risk of platelet transfusion. However, apheresis platelet units have been shown

to have lower risk of infection in the United States. This risk is derived from a decreased number of venipunctures of donors. European studies have failed to demonstrate a similar benefit [88].

Cryoprecipitate is a product of FFP that contains factor VIII, von Willebrand factor, fibrinogen, fibronectin, factor XIII, and platelet microparticles. Cryoprecipitate is made after centrifuging thawed plasma and removing the supernatant. It has a shelf life of one year when frozen at −20°C [89]. The American Association of Blood Banks mandates a minimum of 150 mg of fibrinogen per unit. Cryoprecipitate is customarily transfused in 10 unit bags, although this is highly variable. As a result of this practice, patients generally receive 2.5 g of cryoprecipitate per transfusion. Its indications for use and benefits derived from it are controversial. Two studies from the military demonstrate improved survival in patients who received relatively high doses of cryoprecipitate [90,91]. Fibrinogen concentrate, a product licensed for use in many European countries, has also been investigated. Fries et al., in Austria, have demonstrated that blood loss is decreased after administration of fibrinogen in coagulopathic swine with a liver injury [92]. Ex vivo experiments also demonstrated improved clot characteristics after administration of fibrinogen concentrate [93,94]. However, the data for this product are limited and this is a potential area of clinical investigation.

HTS is any sodium chloride solution that is more concentrated than normal saline. Solutions of 3.0%, 5%, and 7.5% are commercially available. However, 7.5% HS is not approved for use in the United States. High concentrations of sodium chloride in the vascular system favor the flux of water from the interstitial space and from the cells to augment the blood volume. This results in a rapid restoration of intravascular volume. Infusions of small amounts of these solutions lead to hemodynamic responses equivalent to much larger volumes of crystalloid solutions. This is advantageous because of the rapidity of the response. In some military and wilderness environments, the smaller and much lighter volume of fluid is a significant advantage logistically. Recent work suggests that these fluids decrease the activation of neutrophils, so they may offer an advantage in preventing multiple organ dysfunction syndrome [95]. The proponents of these fluids believe that the smaller volumes lead to less tissue edema and associated potential complications. Once fluid is drawn into the vascular space, the sodium chloride is diluted, so it then equilibrates across the fluid spaces of the body. As this happens, the effect of the HTS is gradually lost. Increases in mean arterial pressure are short-lived, with hemodynamic effects lasting only 15 to 75 minutes [96]. The largest potential danger with hypertonic solutions is hypernatremia. This may be accentuated in the previously dehydrated patient without additional extravascular fluid to donate to the vascular system. Although some rapid and transient hypernatremia seems to be tolerated, caution in administration and careful monitoring of sodium levels are important in the safe use of these solutions [97].

Vasopressor agents can be useful for achieving a minimal acceptable blood pressure, but typically only after adequate resuscitation. Phenylephrine, dopamine, norepinephrine, and vasopressin are the preferred agents, starting in the lower dose range. If blood pressure and intravascular volume status are acceptable but there is evidence of ongoing hypoperfusion (elevated lactate or base deficit), an inotropic agent such as dobutamine or dopamine can be used. Recent work suggests that adrenal insufficiency is much more common than previously thought, especially in conjunction with etomidate use, and responds well to 2 to 3 days of steroids and vasopressin [98].

In general, the intensivist should approach cardiovascular support in the surgical and trauma patient using the four parameters of hemodynamic performance: (a) preload (best index: pulmonary artery occlusion pressure, "wedge"), (b) afterload (best index: calculated systemic vascular resistance = (mean arterial pressure − central venous pressure [CVP])/cardiac output × 80), (c) cardiac contractility (best index: stroke volume = cardiac output/heart rate), and (d) heart rate. All but heart rate traditionally require invasive monitoring with a pulmonary artery catheter for accurate measurement.

For intravascular volume depletion, hypovolemia, and cardiovascular instability due to sepsis, this manipulation of variables should proceed in the order listed, assuring adequate preload (wedge of 15 to 18 mm Hg) by volume repletion before adjusting other variables (such as adding inotropes for diminished cardiac output). There is, however, a certain cohort of surgical patients who are "nonresponders" to ongoing volume resuscitation. These patients do not vasodilate with initial volume loading. Additional volume loading in the setting of persistent high systemic vascular resistance sets the stage for a problematic tissue edema entity called secondary abdominal compartment syndrome (ACS) wherein intra-abdominal pressure reaches deleterious levels due to "third-spacing" of resuscitation fluid in the abdomen. This occurs in patients without intra-abdominal injuries who require massive resuscitation for injuries in which hemorrhage control is difficult or delayed (e.g., pelvic fractures, mangled extremities). These are the patients who receive 10 to 20 L of crystalloid. In contrast, primary ACS occurs in patients with abdominal injury and the ACS is directly attributed to hemorrhage and tissue response within the abdomen to the primary trauma. Formation of secondary ACS in this group of nonresponders led Balogh and colleagues [99] to decrease DO_2 goal from 600 or more to 500 mL per minute per m^2. The cardiac index and SvO_2 response to this ICU resuscitation protocol and clearance of metabolic acidosis were similar to historic matched controls. The DO_2 600 or more cohort received significantly more crystalloid, had greater incidence of intra-abdominal pressure more than 20 mm Hg (42% vs. 20%; $p < 0.05$), ACS (16% vs. 8%), MOF (22% vs. 9%), and death (27% vs. 11%). The use of plasma has also been linked to avoiding ACS. Cotton et al. demonstrate a significant decrease (from 9.9% to 0%, $p < 0.001$) in the incidence of ACS after implementation of a massive transfusion protocol [65].

MANAGEMENT OF COAGULOPATHY

Ideally decisions regarding management of coagulopathy in trauma, the operating room, or the ICU ideally should be based on laboratory data. Unfortunately, this ideal situation is rarely achieved. Although point-of-care coagulation testing is commercially available via devices designed for home use monitoring of INR, most EDs and ICUs do not have this capability, and they have not been validated in critically injured patients. Patients who have received large amounts of crystalloids, colloids, and/or packed RBCs or other blood components should have a coagulation panel performed that includes PT, activated partial thromboplastin time, INR, and platelet count. When suspicion of consumption and/or dilutional coagulopathy exists, a more complete coagulopathy panel should be performed to include fibrinogen, d-dimer, and fibrin split products. The bleeding patient with thrombocytopenia, hypofibrinogenemia, elevated fibrin split products, and d-dimer should be considered to have a dilutional coagulopathy. We have recently added thromboelastography (TEG) to our coagulation panel.

A recent study by Hess et al. describes the relationship of abnormal coagulation studies and mortality. This paper highlights the connection between injury severity score and coagulopathy, with a linear correlation between the two values. The authors find that an abnormal INR increases the risk of death

from 4.2% to 26.4%. Abnormal aPTT increases the risk from 4.0% to 43.2%. These laboratory values are therefore cheap and reliable indicators of mortality risk, and suggest that early and aggressive treatment of coagulopathy may impact survival [100].

TEG, a simple test developed in 1948 and used primarily in cardiac and transplant surgery, provides a rapid and comprehensive analysis of coagulation status and can likely be used in place of a DIC panel [101–104]. Use of the thrombelastography test is occurring more frequently in trauma patients. In swine TEG has been shown to be a more sensitive test than PT and aPTT, and may be a better test than traditional laboratory tests [105]. TEG has been shown to be better in certain circumstances as it allows testing of blood in its in vivo state temperature rather than warming it up in the laboratory. Watts et al. [106] showed enzyme slowing and decreased platelet function each individually contribute to hypothermic coagulopathy in trauma patients, particularly at body temperatures $< 34^{\circ}C$, whereas such changes were not evident on standard coagulation testing. TEG will likely become more widely used as clinicians become more aware of its usefulness and limitations.

Because prolonged hypotension is a known predisposing factor for the development of coagulopathy after trauma, aggressive resuscitation is the most critical factor in prevention of coagulopathy in the injured patient [107]. Platelets and coagulation factors are consumed with ongoing bleeding. In addition, intravascular volume replacement with crystalloid, colloid, or packed RBCs results in dilution of coagulation factors and platelets, with dilutional thrombocytopenia being the most frequent coagulopathy in trauma patients [108,109]. DCR concepts describe replacing lost intravascular volume with plasma and platelet proteins and minimizing ongoing dilution with excessive crystalloids. Various formulas exist regarding whether to begin with platelets, cryoprecipitate, or FFP when correcting dilutional coagulopathies and regarding when to begin this replacement (e.g., after *n* units of packed RBCs).

Recent studies have investigated the role of activated protein C in traumatic coagulopathy. Brohi et al. describe indirect evidence for consumption of activated protein C as a result of hypoperfusion [110]. Another study by Brohi correlates d-dimer levels, as a corollary of fibrinolysis, with degree of shock and hypoperfusion. This relationship between shock and the anticoagulant and fibrinolytic pathways suggests the need to decrease the severity and duration of shock as a method to manage coagulopathy [111].

If laboratory data are available, they can be used to guide therapy. However in most rapidly bleeding patient's laboratory data returns far too slowly to make intelligent decisions for optimal care. It is this reason that ratio driven transfusion is likely optimal while the patient is bleeding. Once bleeding is controlled, transfusion therapy can convert to laboratory driven parameters. Platelet counts can be obtained to assess need for platelet transfusion (see later discussion), PT/activated partial thromboplastin time to assess need for FFP (if PT or activated partial thromboplastin time are greater than 1.5 times normal), and fibrinogen levels to assess need for FFP (below normal fibrinogen level) and/or cryoprecipitate (fibrinogen levels less than 100 mg per dL). A panel of the aforementioned tests plus fibrin split products and d-dimer demonstrate whether dilutional coagulopathy or fibrinolysis is present. [112]. Conversely, if TEG is available (especially rapid TEG), it likely can be used to drive optimal use of blood products, although these guidelines have not been prospectively validated [113].

Acute hemolytic transfusion reactions, although rare, remain a cause of coagulopathy (from compatibility mismatch). The physician must consider this as a possible inciting cause for DIC, especially when no other cause is apparent. The physician must also be familiar with other less common coagulopathies in the trauma patient (and treatment) such as primary fibrinolysis (epsilon–aminocaproic acid), uremia (desmopressin/1-deamino-8-d-arginine vasopressin), and primary liver disease (FFP and vitamin K). With wider spread of the use of TEG early in trauma resuscitation, the incidence of fibrinolysis is likely to increase.

Platelet counts of less than 20,000 per μL should always be corrected in any bleeding trauma patient being resuscitated, whether or not a life-threatening injury has been identified. If the patient has a known history of aspirin use within the preceding 7 days, ibuprofen or other nonsteroidal anti-inflammatory drug use within the last 2 to 3 days, or an unknown history, it may be necessary to transfuse platelets despite a platelet count greater than 50,000 per μL, particularly in those patients with head injury or those being managed nonoperatively for significant liver or other solid organ injury. Platelet counts of less than 100,000 per μL are a relative indication for platelet transfusion in the head-injured patient with evidence of intracranial hemorrhage, whether as a single-system injury or as part of multisystem injuries. Each unit of platelets transfused can be expected to raise the platelet count by at least 5,000. It is possible that we have been overly restrictive in the use of platelet transfusions, as recent data suggests that increased and early use improves survival, and that keeping platelet counts > 100,000 are associated with improved outcomes [66,89].

Recombinant factor VIIa (rFVIIa) has emerged as an adjuvant to plasma and platelets in the military and has also been extensively studied in civilian trauma centers. However, there exists controversy on timing, appropriate doses, and indications for the use of recombinant factor VIIa [114]. One Level I study on rFVIIa has been published. The primary endpoint for this randomized double-blind clinical trial was blood product use. In blunt trauma patients, a decreased need for RBC transfusion was seen in patients who received rFVIIa (14% vs. 33% required > 20 units of PRBCs, $p = 0.02$). In penetrating trauma, a similar trend was demonstrated, but it did not decrease statistical significance. There were no differences in thrombotic complications between groups and mortality differences were not seen [115]. One military study did demonstrate a survival benefit in patients who received rFVIIa compared to those that did not (14% vs. 35%, $p = 0.01$). Other retrospective studies have demonstrated decreased transfusion requirements with rFVIIa use and no increase in thromboembolic events when matched to controls [116]. Timing of administration has also been studied. The dose of rFVIIa seems to be most effective when given early in a massive transfusion protocol [117]. The use of rFVIIa remains controversial and may be considered as an adjuvant to massive transfusion, based on individual physician preference, although no improvement in survival has been seen.

The early use of plasma and platelets has been demonstrated to improve coagulopathy, although it is unclear why this happens. It seems simplistic to think a minimally improved INR could account for changes in survival or be based on replacing a small percentage of lost coagulation factors. Dente et al.demonstrated an improvement in PT and INR (15.1 ± 0.26 and 1.31 ± 0.29 compared with 17.5 ± 1.1 and 1.72 ± 0.17, $p = 0.04$) with their massive transfusion protocol compared with a historical control group. These benefits were demonstrated on admission to the ICU [118]. Subjectively, using the concepts of DCR has decreased the incidence of coagulopathic bleeding, allowing easier control of surgical bleeding [119]. By identifying patients with coagulopathy secondary to injury, early implementation of an evidenced-based massive transfusion protocol should decrease coagulopathy and improve the possibility of survival. Our recommendation marries the use of a massive transfusion protocol to the tenants of damage control resuscitation. This approach to the severely injured trauma patient will improve survival, but also may present more risk to infection and multi-organ failure. Patients will, however, suffer those complications with the benefit of survival. Critics

of this approach have wisely and appropriately noted the pitfalls of retrospective studies and the potential for survivorship bias. To address these concerns, prospective observational trials are ongoing and randomized control trials are being planned.

PRACTICING DAMAGE CONTROL RESUSCITATION

Damage control resuscitation consists of two components: Hypotensive resuscitation and hemostatic resuscitation [120,121]. Hypotensive resuscitation is a military concept that dates from World Wars I and II, and was resurrected in the early 1990s in Houston. The key is to maximize the resuscitation benefit to the mitochondria while at the same time minimizing rebleeding by not "popping the clot," a strategy that is supported by a significant body of scientific data. This not only preserves the resuscitation fluid within the vascular system but is also logistically sound by preventing needless waste of blood and fluids [20,46,122–127].

Hemostatic resuscitation is a concept centered on the surgical judgment inherent in damage control surgery, namely, "staying out of trouble rather than getting out of trouble" [120,121,128]. By focusing on restoring normal physiology, rather than normal anatomy, this surgical approach has decreased mortality in severely injured trauma patients and has become standard surgical teaching. From a resuscitation viewpoint, the damage control philosophy can be extended to resuscitation, focusing on restoring normal coagulation and minimizing crystalloid and even initial packed RBC resuscitation in the severely injured casualty. Both traditional resuscitation products further dilute the already deficient coagulation factors and can increase MOF [129–139]. The aggressive hemostatic resuscitation techniques described herein should be performed in parallel with equally aggressive and definitive control of bleeding.

PROCESS OF DAMAGE CONTROL RESUSCITATION

The first element of damage control resuscitation is the rapid diagnosis and surgical control of named vessels and gauze packing (standard damage control surgery) in the operating room. Damage control surgery has improved outcomes in severely injured trauma patients [125,128].

Thawed plasma is used as a primary resuscitative fluid, and is started in the ED. This product is shelf-stable for 5 days and thus is available on casualty arrival. This approach not only addresses the metabolic abnormality of shock, but also reverses the coagulopathy present on arrival in the ED. Storing plasma for 5 days does not significantly impair the labile factors (V and VIII), and allows this product to be immediately available for transfusion [140]. The Office of the U.S. Army Surgeon General Blood Bank consultant has recommended use of thawed plasma in theaters and the only two Level 1 trauma centers in the Department of Defense have this product available for their trauma patients [47,120,121].

The packed RBC to plasma ratio of 1:1, early transfusion of platelets, and cryoprecipitate are indicated [141,142]. Coagulopathy is not only present on presentation to the ED but is exacerbated by the "bloody vicious cycle" of hemorrhage leading to crystalloid resuscitation, then hemodilution and hypothermia, followed by further hemorrhage, and so on [48,49,52]. Furthermore, transfusion of large amounts of preserved RBCs contributes to a dilutional coagulopathy, which is primarily the result of thrombocytopenia and poor platelet function [129–131]. In addition, compared to fresh blood cells, stored platelets demonstrate decreased thrombotic function, primarily due to a decrease in expression of high-affinity thrombin receptors during platelet storage [143].

End Points of Resuscitation

The search has been to find this "holy grail" of resuscitation: a better end point of adequate resuscitation than heart rate, blood pressure, or urine output. Cardiac output, venous return, low perfusion, and acidosis were all observed in Cannon's original shock experiments [122,144]. Urine output is often used as a surrogate marker of adequate resuscitation of an end organ, but has several drawbacks as a lone marker of adequacy of resuscitation. Resuscitation to normal levels of oxygen delivery and oxygen consumption were seen as possible goals of resuscitation, but even using these parameters, a significant number of patients proceeded to organ failure and death.

Lactate that accumulates with a lack of tissue oxygenation correlates with base deficit in hemorrhagic shock. Correction of an elevated serum lactate or base deficit is viewed as a better, if not the best, end point for resuscitation of hemorrhagic shock [145]. One criticism of using the base deficit is that its recovery lags behind resuscitation, it is complicated by excess chloride, and its continued pursuit of a normal value leads to overresuscitation. Serum lactate elevation has also been criticized as being too broad a test, and it does not portray what goes on at the cellular level.

Therefore, other techniques that include subcutaneous or intraluminal oxygen tension probes and gastric or luminal wall pH probes have all been described to show end-organ resuscitation [146–148]. Most recently, the use of near-infrared spectroscopy has shown promise in identifying patients in shock, but it remains to be seen if these indices can be used to judge adequacy of resuscitation from shock [149,150]. They all have their benefits, but they are variously invasive and expensive in relation to serum base deficit and lactate. At this time, their impracticality precludes their generalized use [151].

CONCLUSIONS

The thoughtful intensivist balances all needs of the patient when using blood products, fluids, and drugs in the resuscitation of patients in shock. Volume replacement is given for lost volume. Oxygen-carrying capacity replaces lost RBCs, and coagulopathy is reversed with hemostatic replenishment. Judicious use of steroids, pressors, and metabolic control are

TABLE 158.2

SUMMARY OF ADVANCES IN MANAGING RESUSCITATION BASED ON RANDOMIZED CONTROLLED CLINICAL TRIALS

- A restrictive transfusion strategy is at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of acute myocardial infarction and unstable angina patients [5].
- Factor VIIa decreased transfusions with *trends* toward decreased mortality and critical complications [115].
- Gastric mucosal pH may be an important marker of resuscitation and may provide an early warning for systemic complications in the postresuscitative period [148].
- Etomidate use results in temporary and reversible adrenal insufficiency, responsive to vasopressin and steroids [98].

the order of the day. The effect of each treatment is carefully monitored for its impact on the patient in a stepwise fashion, all the while monitoring indicators of tissue perfusion. Interventions are crisply applied and then removed on the basis of critically and serially evaluated data.

Research must continue to focus on rapid surgical control of hemorrhage and the use of hemostatic adjuncts. Research should also consider the immunologic and coagulation response of the body when creating a better fluid for initial resuscitation, such as an oxygen-carrying product, and the identification of accurate measurements of adequate resuscitation. The overarching metabolic milieu, including adrenal function, glucose control, and response to vasoactive medications, must also be carefully studied for best practices and best combination therapies, including dose–response effects. Finally, identifying the best marker or, better yet, combination of markers to prove adequacy of resuscitation deserve thorough study. The risks and benefits of given therapies must be thoughtfully balanced, given the needs of the patient in a particular situation.

Advances in managing resuscitation, based on randomized controlled trials or meta-analyses of such trials, are summarized in Table 158.2.

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CHAPTER 159 ■ THE MANAGEMENT OF SEPSIS

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Sepsis is among the most common reasons for admission to medical ICUs throughout the world. Over the last two decades, the incidence of sepsis in the United States has trebled and is now the 10th leading cause of death [1,2]. Advances in medical technologies, the increasing use of immunosuppressive agents, and the aging of the population have contributed to the exponential increase in the incidence of sepsis. In the United States alone, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal [1,2]. Septic patients are generally hospitalized for extended periods, rarely leaving the ICU before 2 to 3 weeks. Despite the use of antimicrobial agents and advanced life support, the case fatality rate for patients with sepsis has remained between 20% and 30% over the last two decades [1,2]. This chapter provides an overview of this vast topic with particular emphasis on the management of severe sepsis and septic shock.

DEFINITIONS

Sepsis originally meant "putrefaction," a decomposition of organic matter by bacteria and fungi. Since then, a wide variety

of definitions have been applied to sepsis, including sepsis syndrome, severe sepsis, septicemia, and septic shock [3]. In 1991, the American College of Chest Physicians/Society of Critical Care Medicine developed a new set of terms and definitions to define "sepsis" in a more precise manner [4]. The definitions take into account the findings that sepsis may result from a multitude of infectious agents and microbial mediators and may not be associated with actual bloodstream infection. Although the use of these criteria has been criticized and a "newer" diagnostic schema has been suggested (PIRO, which stands for predisposition, insult infection, response, organ dysfunction), these criteria still provide a useful framework to approach patients with infectious diseases [5]. The term "systemic inflammatory response syndrome" (SIRS) was coined to describe the common systemic response to a wide variety of insults. It is characterized by two or more of the following clinical manifestations: (a) a body temperature of $>38^{\circ}C$ or $<36^{\circ}C$; (b) a heart rate greater than 90 beats per minute; (c) tachypnea, as manifested by a respiratory rate of greater than 20 breaths per minute; (d) an alteration of the WBC count of greater than 12,000 cells per mm^3, less than 4,000 cells per mm^3 or the presence of greater than 10% immature neutrophils. When the SIRS is the result of a confirmed infectious process, it is termed "sepsis." Severe sepsis is defined as sepsis plus either organ dysfunction or evidence of hypoperfusion or hypotension. Septic shock is best defined as systolic pressure less than 90 mm Hg (or a fall in systolic pressure of >40 mm Hg) or a mean arterial pressure less than 65 mm Hg after a crystalloid fluid challenge of 30 mL per kg body weight (approximately 2,000 mL) in patients with sepsis and in the absence of other causes for hypotension [6]. In a patient previously known to have a low baseline blood pressure, septic shock is defined as a 30% or greater drop in the mean arterial pressure.

Three stages in the hierarchy of the host's response to infection was therefore recognized, namely, sepsis, severe sepsis and septic shock, with sepsis having the best prognosis and septic shock the worst. Data from recently published trials support this postulate, with the mortality from sepsis ranging from 10% to 15%, severe sepsis from 17% to 20% and septic shock from 43 to 54% [6]. The distinction between severe sepsis and septic shock is critically important as it stratifies patients into groups with a low and high risk of dying respectively. It also suggests that a more aggressive treatment strategy may be indicated in patients with septic shock (see Fig. 159.1).

In patients with shock, the serum lactate has long been recognized to be a marker of disease severity and to be useful for disease stratification [7,8]. Septic patients with a lactate above 4 mmol per L are at an increased risk of death and warrant a more aggressive approach to resuscitation [9–11]. In addition the rate of lactate clearance has been demonstrated to be a good prognostic marker [12].

SITES OF INFECTION AND BACTERIOLOGY

The microbiology and primary sources of infection have undergone a remarkable transition over the past 30 years. The predominant pathogens responsible for sepsis in the 1960s and 1970s were Gram-negative bacilli; however, over the last few decades there has been a progressive increase in the incidence of sepsis caused by Gram-positive and opportunistic fungal pathogens [1]. Data from the large sepsis trials published during the last decade indicate that Gram-positive and Gram-negative pathogens are responsible for about 25% of infections each, with a further 15% due to mixed Gram-positive, Gram-negative organisms, with fungal pathogens accounting for between 5% and 10% of cases. This evolution in the spectrum of pathogens has been associated with an increase in the incidence of multiresistant organisms. Although the abdomen was the major source of infection from 1970 to 1990, in the last two decades pulmonary infections have emerged as the most frequent site of infection.

PATHOGENESIS OF SEPSIS

The pathogenesis of sepsis is exceeding complex and involves an interaction between multiple microbial and hosts factors. Indeed, after exposure to both Gram-negative and Gram-positive bacteria, macrophages upregulate the expression of over 1,000 genes (and proteins) and downregulate an excess of 300 genes, the net result depending on the complex interrelated interaction of these factors [13]. With advances in molecular biology many of the mysteries of sepsis are being unraveled; however, we have only just embarked on our journey along the "sepsis superhighway." The reader is referred to many excellent reviews on this topic [14–19]. Essentially as noted by William Osler in 1921 "*except on a few occasions the patient appears to die from the body's response to infection rather than from it*" [20]. Sepsis can be viewed as an excessively exuberant proinflammatory response with increased production of proinflammatory mediators with activation of leukocytes, mononuclear cells, and the coagulation cascade. The end result is widespread microvascular and cellular injury. The cellular injury results in alteration of cellular and subcellular membranes and receptors, activation of intracellular enzymes, increased apoptosis, mitochondrial dysfunction, and sepsis-related immunosuppression. The excessive proinflammatory responses together with activation of the coagulation cascade are believed to be fundamental events resulting in a systemic microvascular injury. The systemic microvascular injury is a defining characteristic of sepsis and is believed to play a major pathophysiologic role in the progressive organ dysfunction of sepsis.

ORGAN SYSTEM INVOLVEMENT IN SEPSIS

The Hemodynamic Derangements of Sepsis

Sepsis is characterized by a complex combination of cardiovascular derangements, including vasodilation, hypovolemia, myocardial depression, and altered microvascular flow. In volume resuscitated patients with septic shock, systemic vascular resistance is usually low, contractility and biventricular ejection fractions are reduced while ventricular dimensions and heart rate are increased. Despite these changes, volume resuscitated patients typically have a hyperdynamic circulation with a high cardiac output. However, recent data suggest that up to 60% of patients with septic shock may have a hypodynamic circulation with a deceased ejection fraction ($<45\%$) and global left ventricular (LV) hypokinesia [21]. Furthermore, increasing evidence suggests that patients with sepsis develop structural injury to the contractile apparatus of the heart that may contribute to the myocardial dysfunction in sepsis. This is evident by elevated levels of troponin and B-type natriuretic peptide in patients with sepsis [22–24]. Estimates of LV ejection fraction correlate negatively with increased levels of cardiac troponin in patients with septic shock. These data suggest that all patients with sepsis should undergo serial echocardiography to characterize the hemodynamic pattern, as this impacts on the approach to the use of vasopressor and inotropic agents [21]. In addition, cardiac troponin should be measured to assess the degree of myocardial injury.

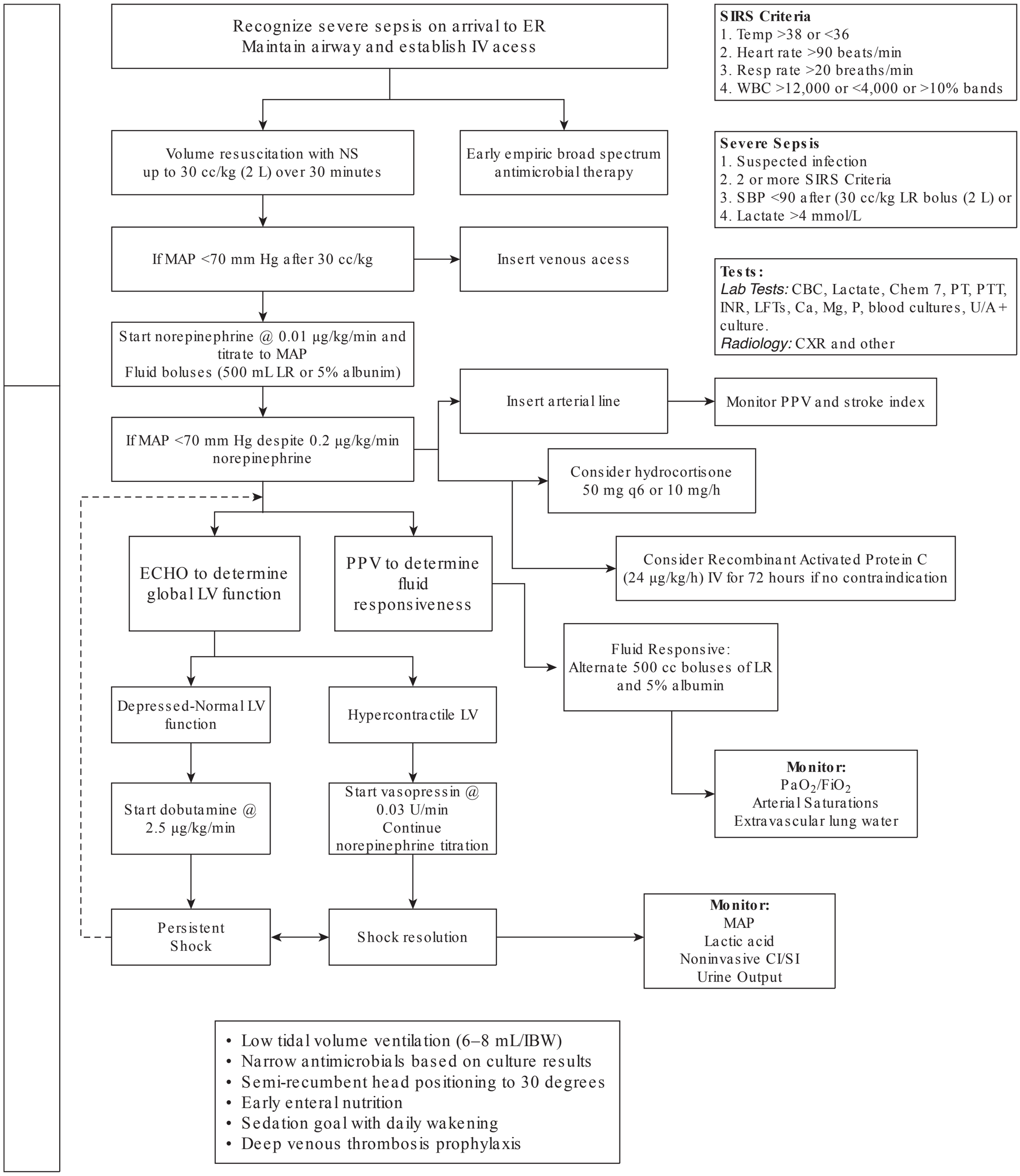

FIGURE 159.1. Suggested approach to the management of patients with severe sepsis and septic shock. CBC, complete blood cell count; CI, cardiac index; CXR, chest x-ray; ER, emergency room; IBW, ideal body weight; ICU, intensive care unit; IV, intravenous; LFTs, liver function tests; LR, lactated Ringer's solution; LV, left ventricle; MAP, mean arterial pressure; NS, normal saline; PPV, pulse pressure variation; PT, prothrombin time; SBP, systolic blood pressure; SI, stroke index; SIRS, systemic inflammatory response syndrome; PTT, partial thromboplastin time; WBC, white blood cell.

Coagulation Activation

Activation of the coagulation cascade with the generation of fibrin is a pathologic and physiologic hallmark of sepsis that occurs in both the intravascular and extravascular compartments [25]. Intravascular coagulation is characterized by diffuse microvascular thrombosis that contributes to widespread ischemic organ damage. Activation of coagulation during sepsis is primarily driven by the tissue factor pathway. Fibrin formation in sepsis likely results from both increased fibrin generation and impaired fibrin degradation. Inhibition of fibrinolysis

is primarily due to increases in plasminogen activator inhibitor-1 (PAI-1). Downregulation of the anticoagulant Protein C pathway also plays an important role in the modulation of coagulation and inflammation in sepsis. Because activation of the coagulation cascade almost all septic patients are thrombocytopenic (or have a falling platelet count), and indeed a normal platelet count makes the diagnosis of sepsis unlikely. An elevated D-dimer, thrombin–antithrombin complexes and a prolonged prothrombin time are found in the majority of patients with severe sepsis while antithrombin, protein C, and protein S levels are significantly decreased. Replacement of coagulation factors with fresh frozen plasma ([FFP] and cryoprecipitate if the fibrinogen is less than 100 mg per dL) is only indicated in patients with clinical evidence of bleeding. Although it had previously been assumed that such therapy "fuels the fire of DIC," there is no evidence that the infusion of plasma products stimulates the ongoing activation of coagulation [26].

Pulmonary

Sepsis is by far the most common cause of the acute respiratory distress syndrome (ARDS) [27–29]. The mortality rate for patients with sepsis complicated by ARDS has been reported to be as high as 60%. The pathophysiology and management of patients with ARDS has been extensively reviewed in the literature.

Renal

Acute renal failure is a serious complication in patients with sepsis. Despite improvements in the support of these patients, the mortality rate remains consistently above 50%. It is, therefore, essential that all patients with sepsis be aggressively resuscitated in an attempt to prevent this complication. The pathogenetic mechanisms leading to ARF in patients with sepsis are unclear ;however, mediator-induced cytotoxicity, alterations in renal perfusion and apoptosis have been suggested [30,31].

Gastrointestinal

The most important gastrointestinal complications occurring in patients with sepsis include gastric stress ulceration, a diffuse splanchnic mucosal injury with increased intestinal permeability and intrahepatic cholestasis.

Nervous and Musculoskeletal

Septic encephalopathy is an acute, reversible, generalized disturbance in cerebral function [32,33]. Septic encephalopathy is essentially a diagnosis by exclusion as many factors such as sedative drugs, encephalitis, liver or renal failure, hypoperfusion, fever, adrenal insufficiency, cerebral vascular accidents, and drug fever either alone or in combination may result in disturbed cerebral function. Electroencephalography is useful in confirming the diagnosis of septic encephalopathy and allows assessment of the severity of the encephalopathy. Treatment is essentially supportive.

Critical illness polyneuropathy (CIP), as initially described by Bolton et al. in 1984, is a sensorimotor polyneuropathy that is often a complication of sepsis and multiorgan failure, occurring in 70% of such patients [34–36]. Postmortem examination of peripheral nerve specimens from patients with CIP has shown primary degeneration of motor and sensory nerves that supply the limbs and respiratory system. Although this denervation is more widespread and severe in the distal muscle groups, the phrenic nerve, diaphragm, and intercostals muscles are also involved. Classically, CIP is associated with a symmetric predominantly distal paresis, with legs involved worse than arms, along with impaired sensory testing in the feet and hyporeflexia. CIP is difficult to diagnose clinically and is often suspected when critically ill patients are otherwise improving yet continue to have difficulty in weaning from mechanical ventilation.

In addition to neuropathy, weakness in critically ill septic patients may stem from disturbances in the structure or function of muscle per se. According to biopsy and neurophysiologic studies, myopathies occur much more frequently during critical illness than was previously recognized. Myopathic changes have been demonstrated by electromyographic examination and biopsy in many septic ICU patients. The changes are often mild and usually accompany CIP. In other patients however, myopathy is the predominant finding. This myopathy has been called critical illness myopathy.

Sepsis and Multisystem Organ Dysfunction

The ultimate cause of death in patients with sepsis is multiple organ failure. Typically, patients will first develop a single organ failure and then, if the disease remains unchecked, will progressively develop failure/dysfunction of other organ systems. There is a close relationship between the severity of organ dysfunction on admission to an ICU and the probability of survival. The pathogenesis of organ dysfunction is multifactorial and incompletely understood. Tissue hypoperfusion and hypoxia are dominant factors. Multisystem organ dysfunction has an extraordinarily high mortality and, for many patients, the support of this syndrome does not improve survival but rather prolongs the dying process.

CLINICAL FEATURES AND DIAGNOSIS OF SEPSIS

Sepsis is a systemic process with a variety of clinical manifestations. The initial symptoms of sepsis are nonspecific and include malaise, tachycardia, tachypnea, fever, and sometimes hypothermia. Although most patients with sepsis have an elevated white cell count, some patients present with a low white cell count, which in general, is a poor prognostic sign. A band count in excess of 10% has been reported to have a high specificity (92%) but low sensitivity for the diagnosis of sepsis (43%) [37]. Other clinical manifestations include altered mental status, hypotension, respiratory alkalosis, metabolic acidosis, hypoxemia with acute lung injury, thrombocytopenia, consumptive coagulopathy, proteinuria, acute tubular necrosis, intrahepatic cholestasis, elevated transaminases, hyperglycemia, and hypoglycemia. Patients may present with clinical features of a localized site of infection, such as cough, tachypnea and sputum production due to pneumonia; flank pain and dysuria with urinary tract infection and abdominal pain with intra-abdominal infection.

The manifestations of sepsis can sometimes be quite subtle, particularly in the very young, the elderly, and those patients with chronic debilitating or immunosuppressing conditions. These patients may present with normothermia or hypothermia. The failure to generate a temperature greater than 99.6°F (37.5°C) in the first 24 hours of clinical illness, has been associated with an increased mortality rate. An altered mental state or an otherwise unexplained respiratory alkalosis may be the presenting feature of sepsis.

The signs and symptoms of systemic inflammation are not useful in distinguishing infectious from noninfectious causes of SIRS. Furthermore, a bacterial pathogen is not isolated in

all patients with sepsis. Consequently, a number of biomarkers have been evaluated as more specific indicators of infection, including procalcitonin (PCT) and triggering receptor expressed on myeloid cells (TREM-1). PCT, a propeptide of calcitonin, is normally produced in the C-cells of the thyroid. In healthy individuals, PCT levels are very low (< 0.1 ng per mL). In patients with sepsis, however, PCT levels increase dramatically, sometimes to more than several hundred nanograms per milliliter. The exact site of PCT production during sepsis is uncertain; however, mononuclear leukocytes and the liver seem to be the major sources of PCT. TREM-1 is a monocyte receptor that is upregulated by bacterial and fungal pathogens [38]. The ligand for TREM-1 is unknown. A soluble form of TREM-1 (sTREM-1) is released from activated phagocytes and can be found in body fluids. The use of these biomarkers has not gained widespread acceptance presumable due to the cost of the tests and the uncertain diagnostic accuracy.

Blood cultures are considered to provide the clinical gold standard for the diagnosis of bacterial infections. However, blood cultures are only positive in between 20% and 30% of patients with sepsis; moreover, it takes 2 to 3 days before the results become available. Molecular methods based on polymerase chain reaction (PCR) technology have been developed for infection diagnosis and pathogen identification. These methods offer a new approach based on detection and recognition of pathogen DNA in the blood, or indeed other clinical samples, with the potential to obtain results in a much shorter time frame (hours) than is possible with conventional culture. PCR based pathogen detection depends on the ability of the reaction to selectively amplify specific regions of DNA, allowing even minute amounts of pathogen DNA in clinical samples to be detected and analyzed. This technique holds great promise and may revolutionize our approach to the diagnosis of bacterial, fungal, and viral infections.

MANAGEMENT OF SEPSIS

The management of patients with severe sepsis and septic shock is complex requiring multiple concurrent interventions with close monitoring and frequent re-evaluations. These patients are best managed in intensive care units by physicians experienced in the management of critically ill septic patients. The reader is referred to the "*Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock*"; these guidelines were developed by a number of international critical care organizations and should serve as the framework for the management of patients with sepsis [10].

The current strategy for the management of patients with sepsis is largely based on treating or eliminating the source of infection, timely and appropriate usage of antimicrobial agents, hemodynamic optimization, and other physiologic organ supportive measures (see Table 159.1). Attempts at downregulating the proinflammatory response with novel agents directed at specific proinflammatory mediators has uniformly met with failure. However, both activated protein C (APC) and glucocorticoids (low dose) are immunomodulators that have been demonstrated to improve the outcome of patients at high risk of death.

TABLE 159.1

SUGGESTED FLUID RESUSCITATION ALGORITHM FOR HEMODYNAMIC INSTABILITY OF SEVERE SEPSIS AND SEPTIC SHOCK

1 L Normal Saline 15–20 minutes
1 L 30 minutes
Start Norepinephrine if MAP ≤ 70 mm Hg
1 L 500 cc 5% albumin over 30–40 minutes
1 L Ringers 30–40 minutes
1 L 500 cc 5% albumin over 30–40 minutes
Ringers lactate 200 cc/h
Bolus 500 cc 5% albumin or Ringers Lactate

It has become increasingly apparent that in many patients there is a long delay in both the recognition of sepsis and the initiation of appropriate therapy. This has been demonstrated to translate into an increased incidence of progressive organ failure and a higher mortality. Kumar et al. investigated the relationship between the duration of hypotension prior to antimicrobial administration in 2600 patients with sepsis induced hypotension [39]. They reported that the risk of dying increased progressively with time to receipt of the first dose of antibiotic. Furthermore, there was a 5% to 15% decrease in survival with every hour delay over the first 6 hours. In the ENHANCE study, the mortality was 33% if drotrecogin alpha-activated (APC) was given within the first 24 hours of admission as compared to 52% if it was given on day 3 of hospitalization [40].

Levy et al. retrospectively analyzed the Sequential Organ Failure Assessment scores during the first 48 hours in 1,036 severely septic patients [41]. From baseline to day 1, the direction of change in cardiovascular, renal, respiratory, hematologic, and hepatic functions independently predicted 28-day mortality. The implications of this study is that if organ dysfunction is not improving during the first day of severe sepsis, the mortality risk is significantly increased, underscoring the importance of early recognition and therapeutic intervention to prevent sequential organ dysfunction [42]. Similarly, Rivers et al. demonstrated that early (within 6 hours) clearance of lactate is associated with improved outcome in severe sepsis and septic shock [12].

The concept that early aggressive treatment (within the first 6 hours of admission to hospital) of patients with severe sepsis and sepsis shock reduces sequential organ failure and improves survival has been demonstrated in the "landmark" study by Rivers et al. [43]. In this study, *early aggressive therapy* that optimized cardiac preload, afterload, and contractility in patients with severe sepsis and septic shock improved survival. The patients in the early-therapy group received, on average, approximately 1,500 mL more in total fluids in the first 6 hours of treatment than did the standard-therapy group and had a significantly higher mean arterial pressure (mean [± SD], 95 ± 19 vs. 81 ± 18 mm Hg; $p < 0.001$). Mortality was 30.5% in the group receiving early goal-directed treatment, as compared with 46.5% in the control group ($p = 0.009$). This strategy for managing patients with severe sepsis and septic shock has been called "early goal-directed therapy (EGDT)."

While the concept of early, as opposed to delayed, volume resuscitation and the timely initiation of appropriate antibiotics in patients suffering from severe sepsis and septic shock is a scientifically sound concept, the author believes that the major pillars on which EGDT is based (central venous pressure [CVP] > 8 mm Hg, $ScvO_2$ > 70% and blood transfusion) may be flawed (see later) [44]. A more evidence-based approach is provided in Figure 159.1.

Identification and Eradication of the Source of Infection

One of the most challenging features of the sepsis syndrome is that of identifying and eradicating, as early as possible, the source of infection. The majority of patients presenting with severe sepsis usually have a pulmonary, genitourinary, primary blood stream, intra-abdominal, or intravenous catheter as a source of infection. Recent studies have demonstrated that in approximately 75% of patients with presumed sepsis, an

etiological agent can be isolated, these being equally divided amongst Gram-positive and Gram-negative organisms. It has been known for centuries that, unless the source of the infection is controlled, the patient cannot be cured of his or her infective process and that death will eventually ensue. Surgical control or percutaneous drainage of the infective process is therefore essential in most patients with severe intra-abdominal infections; recovery will not occur without them. Infected central venous catheters must be removed from patients with catheter related sepsis [45].

Antimicrobial Agents

Antimicrobial therapy remains the cornerstone of treatment in patients with sepsis. Empiric intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. The choice of antibiotics is largely determined by the source or focus of infection, the patient's immunologic status, whether the infection is nosocomial or community acquired as well as knowledge of the local microbiology and sensitivity pattern. Initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that penetrate into the presumed source of sepsis. Because the identity of the infecting pathogen(s) and its sensitivity pattern(s) are unknown at the time of initiation of antibiotics, patients with severe sepsis and septic shock the initial regimen should include two or more antibiotics or an extended spectrum β-lactam antibiotic. A number of studies have demonstrated that appropriate initial antimicrobial therapy, defined as the use of at least one antibiotic active in vitro against the causative bacteria reduced mortality when compared with patients receiving inappropriate therapy [45,46]. Once a pathogen is isolated, monotherapy is adequate for most infections; this strategy of initiating broad-spectrum cover with two or more antibiotics and then narrowing the spectrum to a single agent when a pathogen is identified is known as "antimicrobial de-escalation." The indications for continuation of double-antimicrobial therapy include enterococcal infections and severe intra-abdominal infections. The role of double-antimicrobial therapy with a β-lactam antibiotic and aminoglycoside in patients with suspected or proven *Pseudomonas aeruginosa* infections is unclear; however, double coverage is prudent in immunocompromised patients [47,48]. In patients with culture-negative sepsis, continuation of the initial empiric combination is warranted. Additional antibiotics or a change in antibiotics may be required in patients with culture-negative sepsis who do not appear to be responding to the initial empiric regimen.

Although monotherapy is considered standard for community-acquired pneumonia, a survival benefit of a combination β-lactam and macrolide has been suggested. Waterer et al. found that patients with bacteremic pneumococcal disease who receive at least two effective antibiotic agents within the first 24 hours after presentation to hospital had a significantly lower mortality than patients who received only one effective antibiotic agent [49]. The most common combination was a third-generation cephalosporin with a macrolide or quinolone. Using a large hospital database, Brown et al. demonstrated a lower mortality, shorter length of stay and lower hospital charges for patients with community-acquired pneumonia treated with dual therapy using macrolides as the second agent [50].

To rapidly achieve adequate blood and tissue concentrations, antibiotics should be given intravenously, at least initially. Dosing regimens should take into account whether the antibiotic "kills" by time-dependent kinetics (e.g., β-lactam antibiotics, vancomycin) or concentration-dependent kinetics (e.g., aminoglycoside) [51,52]. The clinical effectiveness of β-lactam antibiotics and vancomycin is optimal when the concentration of the antimicrobial agent in the serum exceeds the minimum inhibitory concentration of the infecting organism for at least 40% of the dosing interval. In addition, antibiotic dosing should also take into account the patient's hepatic and renal function.

Chastre et al. performed a study in which patients with ventilator associated pneumonia were randomized to receive either 8 or 15 days of antibiotics [53]. Those treated for 8 days had neither excess mortality nor more recurrent infections, although those with nonfermenting Gram-negative bacilli did have a higher pulmonary infection recurrence rate. Antibiotics should therefore be continued until clinical improvement is noted and ordinarily should not be continued for more than 10 days (14 days for *P. aeruginosa* and Acinetobacter species), except in cases of osteomyelitis and endocarditis.

Hemodynamic Support

Fluid Resuscitation: Initial Versus Late

In the first hours of severe sepsis, venodilatation, transudation of fluid from the vascular space into the tissues, reduced oral intake and increased insensible loss combine to produce hypovolemia. Along with ventricular dysfunction, and arteriolar dilation volume depletion contributes to impaired global perfusion and organ function. Treating hypovolemia is the most important component of the early management of severe sepsis. However, once the patient has received an adequate fluid challenge (3 to 5 L) further fluid challenges may not increase cardiac output and global perfusion. Additional fluid may increase interstitial edema and further comprise the microvascular dysfunction that characterizes severe sepsis. The current paradigm of fluid management in patients with sepsis is one of adequate initial fluid resuscitation followed by conservative late fluid management. Conservative late fluid management is defined as even-to-negative fluid balance measured on at least two consecutive days during the first 7 day after septic shock onset. In a retrospective cohort study, Murphy et al. demonstrated that an approach that combines both adequate initial fluid resuscitation followed by conservative late fluid management was associated with improved survival [54]. Additional studies have demonstrated that those patients who have a smaller cumulative fluid balance have improved clinical outcomes [55–57].

Although the type of fluid used in the resuscitation of patients with sepsis has not been definitively shown to affect outcome, subgroup analysis of the SAFE study suggested a trend towards a more favorable outcome in patients who received albumin [58]. This finding is supported by experimental studies [59] and patients with malaria (similar pathophysiology to Gram-negative sepsis) [60]. Albumin has a number of properties that may be advantageous in patients with sepsis including the maintenance of the endothelial glycocalyx and endothelial function as well as having antioxidant and anti-inflammatory properties that may translate into less "third" space fluid loss. Hydroxyethyl starch solutions were previously recommended in patients with sepsis; however, these synthetic colloids have recently been demonstrated to be associated with an increased risk of renal failure (and death) and should therefore be avoided in patients with sepsis [61]. Despite differences in composition, normal saline (NS) and Lactated Ringer's solution (LR) are frequently considered equivalent and lumped under the term "balanced salt solution." However, both experimental and clinical data have demonstrated that these fluids are not equivalent. Studies have demonstrated the development of a hyperchloremic metabolic acidosis in human volunteers and patients

resuscitated with normal saline [62–65]. Although the clinical implications of this finding are unclear, the additional loss (renal) of HCO_3 in the setting of reduced buffering capacity only adds to the acid–base burden characteristic of hypoperfused states [63]. Furthermore, resuscitation with normal saline may produce a "dilutional acidosis." Many erroneously believe that LR may worsen or cause a "lactic acidosis." This is impossible as lactate (the base) has already donated H+ ions; indeed, LR is converted to glucose (mainly in the liver). This reaction consumes hydrogen ions, thereby generating HCO_3 [66]. Although, the lactate concentration (base) may increase with LR, this increase is associated with an increase in HCO_3 and an increase in pH (even with liver disease). This observation was elegantly demonstrated by Phillips et al. in a swine hemorrhagic shock model; the results demonstrated a significantly higher pH (7.41 vs. 7.17) in animals resuscitated with LR as compared to normal saline [67]. In addition to its effects on acid–base balance, solutions high in chloride have been shown both experimentally and clinically to reduce the glomerular filtration rate (GFR) (due to tubuloglomerular feedback) [68]. The effects of normal saline on acid–base balance and renal function may be dose related. These data suggest that in patients with sepsis (except those with hyperkalemia), LR may be preferable to normal saline. There is however, no outcome data to support this recommendation. Furthermore, it should be noted LR solution is a racemic mixture containing both the L- and D-isomer of lactate. Small animal hemorrhagic shock models have suggested that the D-isomer is proinflammatory and increases apoptotic cell death [69–71]. The clinical implications of these findings are unclear.

On the synthesis of these data, we recommend initial resuscitation with NS (30 mL per kg). Normal saline is preferred until renal function tests and potassium are known. Patients who respond poorly to this initial bolus (± 2 L) may best be fluid resuscitated with alternating boluses (500 mL) of albumin and LR until the hemodynamic goals are achieved (see "The Endpoints of Resuscitation" section and Fig. 159.1). The goal of this approach is to maintain normal acid–base balance, achieve adequate intravascular volume, and yet limit the total amount of fluid given.

Vasopressors, Inotropes, and Cardiac Function

The optimal time to initiate vasopressor agents has not been rigorously studied. Many patients with severe sepsis will respond to a 2-L fluid challenge and require little additional hemodynamic support. Others will remain hypotensive despite 10 L of fluid (fluid does not increase vascular tone!). The goal of fluid resuscitation is the rapid early restoration of intravascular volume followed by a conservative fluid strategy. We have therefore recommended that a vasopressor agent (norepinephrine) be started once the patient has received 2 L of crystalloid [6,72]. At this point, the norepinephrine (starting at 0.01 µg per kg per minute) should be titrated upwards while fluid resuscitation continues (albumin and LR). Ongoing fluid resuscitation should be guided by mean arterial pressure, pulse pressure variation, urine output, oxygenation as well as cardiac output (determined noninvasively), and extravascular lung water measurement [73,74]. Bedside echocardiography is very useful to determine LV size and function. The CVP neither intravascular volume nor does it predict fluid responsiveness and therefore has no place in the resuscitation of patients with sepsis [75].

Although there are little data to suggest that one vasopressor results in better outcomes than another (norepinephrine, epinephrine, vasopressin) [76–78], we favor norepinephrine as the first-line agent followed by dobutamine or epinephrine in patients with poor LV function and vasopressin (fixed dose of 0.03 U per minute) in patients with "preserved" LV function and a low systemic vascular resistance (see Fig. 159.1). In patients with sepsis, norepinephrine increases blood pressure, as well as cardiac output, renal, splanchnic, cerebral blood flow, and microvascular blood flow while minimally increasing heart rate [79,80]. Norepinephrine would therefore appear to be the ideal fist-line agent for the management of septic shock; additional agents should be considered in patients who remain hypotensive or display evidence of inadequate tissue or organ perfusion despite doses of norepinephrine up to 0.2 µg per kg per minute. The second/third-line agents should be chosen based on the patient's hemodynamic profile as determined by ECHO and noninvasive assessment of cardiac output.

Dopamine has a number of theoretical disadvantages in patients with sepsis. It tends to increase heart rate that increases myocardial oxygen demand and is associated with splanchnic mucosal ischemia. In addition, dopamine inhibits T and B lymphocytes and decreases secretion of prolactin, growth hormone, and TSH. The SOAP study suggested that septic patients who received dopamine had an increased mortality when compared with other vasopressors [81]. This drug should therefore be avoided in patients with sepsis. Similarly phenylephrine is not recommended, as in experimental models it decreases cardiac output as well as renal and splanchnic blood flow [82]. Furthermore, these agents have not been rigorously tested in randomized controlled studies.

The Endpoints of Resuscitation

The optimal "hemodynamic" endpoint of resuscitation in patients with sepsis is unknown. Similarly, the target mean arterial pressure (MAP) is controversial. Traditional teaching suggests that we should achieve a MAP above 60 mm Hg. However, this pressure is below the autoregulatory range of a number of organs, particularly in elderly patients with atherosclerotic disease. The *Surviving Sepsis Campaign* Guidelines suggest targeting a MAP above 65 mm Hg [10]. In a dose escalation study, Jhanji et al. incrementally increased the dose of norepinephrine to achieve a MAP of 60, then 70, then 80, and lastly 90 mm Hg [80]. In this study, global oxygen delivery, cutaneous microvascular flow, and tissue oxygenation increased with each sequential increase in MAP. However, LeDoux et al. demonstrated that increasing the MAP from 65 to 85 mm Hg with norepinephrine did not significantly affect systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchnic perfusion [83]. Dubin demonstrated that increasing mean arterial pressure from 65 to 75 and 85 mm Hg did not improve microcirculatory blood flow [84]. Similarly, Bourgoin et al. demonstrated that increasing MAP from 65 to 85 mm Hg with norepinephrine neither affected metabolic variables nor improved renal function [85]. However, Derudre et al. demonstrated that in patients with septic shock when the MAP was increased from 65 to 75 mm Hg, urinary output increased significantly while the renal resistive index significantly decreased [86]. These data suggest that although the endpoint of resuscitation should be individualized, a MAP of 65 to 70 mm Hg may be a reasonable initial target.

Central venous oxygen saturation ($ScvO_2$) is used as the endpoint of resuscitation in the EGDT algorithm [43]. This is problematic for a number of reasons. Septic patients usually have a normal or increased $ScvO_2$ due to reduced oxygen extraction [87,88]. A normal $ScvO_2$ therefore does not exclude tissue hypoxia [89]. A low $ScvO_2$ is an important sign of inadequate oxygen delivery to meet systemic oxygen demands. However, it provides no information for the reason for this inadequacy, nor does it provide guidance as to the optimal therapeutic approach. It is noteworthy that in the Rivers study the mean $ScvO_2$ was 49% with 65% of patients having a $ScvO_2$ less than 70%. To our knowledge, no other sepsis study has reproduced this finding, with the mean $ScvO_2$ (on presentation)

in most sepsis studies being approximately 70% [89–91]. This suggests that other factors may have been in play to account for the low $ScvO_2$ in the Rivers study [92,93]. These factors include the delayed presentation to hospital (possibly due to socioeconomic factors), greater number of patients with comorbid medical conditions and a high incidence of alcohol use [93]. Thus the combination of significant comorbidities (including heart disease) and a more delayed arrival of patients to the Emergency Department in the River's study may have led to a low cardiac output state, and in turn, to the very low $ScvO_2$ values.

ADJUNCTIVE THERAPIES

While antibiotics, fluid resuscitation, vasopressors/inotropic agents and source control form the basic elements of the management of severe sepsis/septic shock, a number of adjunctive agents have been demonstrated to improve outcome or hold promise in improving the outcome of patients with sepsis. These agents should be considered in patients with severe sepsis/septic shock. The benefit of these agents is, however, time dependent and should be started as soon as possible and always within the first 24 hours of ICU admission

Corticosteroids

While the role of hydrocortisone in patients with septic shock is controversial, hydrocortisone should be considered in patients who require in excess of 0.2 µg per kg per minute of norepinephrine [94,95]. Adrenal function testing is not required in these patients. Evolving data suggest that increased levels of inflammatory mediators persist long after clinical resolution of sepsis [96,97]. Furthermore, abruptly stopping steroids results in a rebound phenomenon with worsening lung inflammation and hypotension These data suggest that the duration of therapy should be guided by the length of the immune dysregulation and should then be followed by a slow taper. Furthermore, the risk/benefit ratio of treatment with glucocorticoids is tightly linked to the dosage used. Although high doses of glucocorticoids blunt all arms of the immune system, stress-doses (200 to 300 mg hydrocortisone Eq per day) inhibit systemic inflammation; yet, maintain innate and Th1 immune responsiveness and prevent an overwhelming compensatory anti-inflammatory response [98,99]. Similarly, although myopathy is common in patients treated with high-dose corticosteroids, this complication is uncommon with stress-doses of corticosteroids. On the basis of these data, we suggest treatment with hydrocortisone in a dose of 50 mg every 6 hourly or a 100 mg bolus followed by an infusion at 10 mg per hour for 10 to 14 days followed by a slow taper.

Activated Protein C

The PROWESS study demonstrated a significant reduction in mortality in patients with severe sepsis and septic shock who were treated with activated protein C (APC) within 24 hours of hospital admission [100]. APC should be considered in patients with septic shock and those with sepsis and at least one organ failure, who are at a high risk of death, particularly patients with severe community-acquired pneumonia [101]. The use of APC in patients with sepsis has, however, become a very controversial and charged issue. This is largely driven by the high rate of serious bleeding that has been reported in retrospective cohort studies [102]. APC should be avoided in patients at high risk of bleeding, including patients with a platelet count of $< 30{,}000$ per mL^3. Although APC increases the partial thromboplastin time (PTT) in vitro, the PROWESS study demonstrated an increased risk of bleeding when the PTT increased above 75 seconds. On the basis of these data, we monitor the PTT in patients on APC and hold the infusion (for a few hours) and transfuse FFP when the PTT exceeds 80 seconds (anecdotal experience only). Disseminated intravascular coagulation (DIC) is not a contraindication to APC; indeed in PROWESS the risk reduction was greater in patients with overt DIC than those without DIC (RR of 0.6 vs. 0.85) [103].

Patients with purpura fulminans and multiorgan failure due to meningococcal infection have significantly higher plasma PAI-1 levels as well as lower protein C levels than patients with meningococcal infection, but without purpura or organ failure [104]. In view of the low protein C levels in purpura fulminans, numerous case reports as well as open label studies have been published suggesting a benefit of treatment with APC [104–106]. Many of these patients concomitantly received FFP, fibrinogen, and platelets. APC has also been used for the treatment of purpura fulminans associated with Streptococcal and Staphylococcal infections [107].

Enteral Nutrition Supplemented with Omega-3 Fatty Acids

Three randomized controlled trials have demonstrated that in patients with sepsis and ARDS an enteral nutritional formula high in omega-3 fatty acids was associated with an increase in ventilator-free days, a shorter ICU stay, and a lower morality than patients fed a diet with a low omega-3 to omega-6 fatty acid ratio [108]. On the basis of these data, an enteral nutritional formula high in omega-3 fatty acids should be initiated within 24 hours of admission to the ICU. Patients are best fed gastrically via an oral or nasogastric tube. The use of vasopressors agents is not a contraindication to the use of enteral nutrition; indeed, enteral nutrition reduces the risk of gastric stress ulceration and bowel ischemia [109,110].

Polyclonal Immunoglobulins

Two meta-analyses have demonstrated that polyclonal immunoglobulins particularly those preparations enriched with IgA and IgM (IgGAM) reduce the mortality in patients with septic shock [111,112]. It is not clear which patient subgroups would benefit from this therapy; clearly asplenic patients should receive IgGAM as well as those patients at high risk of death.

ADJUNCTIVE THERAPIES OF POSSIBLE BENEFIT

Statins

HMG-CoA reductase inhibitors (statins) are a group of drugs with anti-inflammatory, immunomodulating, antioxidant, antiproliferative, antiapoptotic, antithrombotic, and endothelial stabilizing effects. Statins increase expression of endothelial nitric oxide (eNOS) while downregulating inducible nitric oxide (iNOS) [113]. Furthermore, statins interfere with leucocyte–endothelial interactions by decreasing expression of adhesion molecules and have antithrombotic effects. Experimental

sepsis studies have demonstrated improved outcome with the use of statins and clinical studies have demonstrated that patients taking statins have a better outcome when they become septic [113–115]. We recommend the use of high-dose statins (e.g., atorvastatin/simvastatin 80 mg daily) in patients with severe sepsis; statins should however be avoided in patients taking azole antifungal as well as calcineurin inhibitors. The clinician should monitor for rhabdomyolysis.

Selenium

Sepsis is associated with an increase in reactive oxygen species and low endogenous antioxidative capacity. The selenium dependent glutathione-peroxidases (GPx) as well as thioredoxin reductases are important compounds responsible for the maintenance of the redox system in all cells including the immune-competent cells. The activity of these enzymes is mainly regulated by the availability of selenium. The selenium in intensive care (SIC) study demonstrated that high-dose intravenous selenium improved the outcome of patients with severe SIRS, sepsis, and septic shock [116]. Selenium supplementation should be considered in patients with severe sepsis and septic shock. Although the optimal dose and route remain to be established, we recommend a dose of 400 to 600 µg PO daily.

Zinc

Zinc is required for normal function of both the innate and acquired immune systems. Zinc deficiency results in marked abnormalities of immune function with zinc supplementation restoring natural killer cell activity, lymphocyte production, mitogen responses, wound healing, and resistance to infection. Stress, trauma, and sepsis have been associated with very low serum zinc levels [117,118]. In an experimental sepsis model, mortality was significantly increased with zinc deficiency, while zinc supplementation normalized the inflammatory response, diminished tissue damage and reduced mortality [119]. The benefit of zinc supplementation in patients with sepsis has yet to be determined.

CONCLUSION

The last two decades has seen a remarkable growth in our understanding of sepsis and the complex interconnection of multiple biological pathways involved in the septic process. This increased knowledge has opened the door to new therapeutic approaches to sepsis, and it is likely that these new approaches will lead to a reduction in the morbidity and mortality of patients with sepsis.

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CHAPTER 160 ■ MULTIPLE ORGAN DYSFUNCTION SYNDROME

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Care of the critically ill has advanced substantially in the past 50 years to the point that patients who previously succumbed to illness or injury may now survive their initial insult. Unfortunately, this places them at risk for multiple organ dysfunction syndrome (MODS), with subsequent failure of organ systems and increased mortality [1]. A thorough understanding of the pathophysiology and treatment of MODS is necessary to attempt to mitigate associated secondary morbidity and mortality.

MODS can be defined as "the inability of one or more organs to support its activities spontaneously without intervention" [2]. Initial recognition of MODS came from combat casualty care during World War II as resuscitation strategies advanced sufficiently to allow casualties to survive the initial hemorrhagic shock insult, but rendered them vulnerable to subsequent acute renal failure [3]. Improved intensive care and resuscitation strategies subsequently led to the recognition of pulmonary failure in the form of ARDS during the Vietnam conflict [4]. Basic science and clinical research has increased our insight into the role of cellular hypoxia in the development of organ dysfunction and failure. Although advances in support for failing organs, including continuous dialysis and advanced ventilator care, have potentially increased survival, MODS remains a common cause of death in the intensive care unit.

DIAGNOSTIC CRITERIA AND SCORING SYSTEMS

MODS severity determines mortality [5]. Organ failure severity scoring was initially described by Knaus in 1985 [6]. Modern scoring systems consider grade and severity and are intended to serve as predictors of outcome. Among the most commonly used scoring systems are the multiple organ dysfunction score (MODS), sequential organ failure assessment (SOFA) and logistic organ dysfunction score (LODS) [7–9]. All include clinical and laboratory data for six organs: respiratory, cardiovascular, hematologic, hepatic, renal, and central nervous system (Table 160.1) [10]. The Denver Multiple Organ Failure (MOF) score is a simpler 4-point scale that has similar or superior specificity [11]. A "cellular injury score" based on measures of cellular dysfunction has also been described [12]. No single scoring system has been proven superior but all predict outcome more accurately than health care resource utilization [11,13]. The acute physiology and chronic health evaluation (APACHE), originally described by Knaus in 1985, is a scoring system that considers patient factors unrelated to the acute illness as well as acute illness severity [14]. APACHE considers many variables and is therefore not as easily calculable at

TABLE 160.1

CRITERIA USED IN COMMON ORGAN DYSFUNCTION SCORING SYSTEMS

Organ	Variable	Denver MOF [11]	SOFA [8]	LODS [9]	MODS [7]
Respiratory	PaO_2/FIO_2	Yes	Yes	Yes	Yes
	MV		Yes		
Hematology	Platelets		Yes	Yes	Yes
	WBC			Yes	
Hepatic	Bilirubin	Yes	Yes	Yes	Yes
	Prothrombin time			Yes	
Cardiovascular	MAP		Yes		
	SBP			Yes	
	Heart rate			Yes	
	PAR [(HR□CVP)/MAP]				Yes
	Dopamine		Yes		
	Dobutamine		Yes		
	Epinephrine		Yes		
	Norepinephrine		Yes		
	Any inotrope	Yes			
CNS	GCS		Yes	Yes	Yes
Renal	Creatinine	Yes	Yes	Yes	Yes
	BUN			Yes	
	Urine output		Yes	Yes	

Denver MOF, Denver multiple organ failure score; SOFA, sequential organ failure assessment; LODS, logistic organ dysfunction score; MODS, multiple organ dysfunction score; PaO_2, blood partial pressure of oxygen; FIO_2, fraction of inspired gas which is oxygen; MV, mechanical ventilation requirement; WBC, elevated white blood count; PAR, pressure adjusted heart rate; HR, heart rate; CVP, central venous pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; CNS, central nervous system; GCS, Glasgow Coma Scale score; BUN, blood urea nitrogen.
Modified from Mizock BA: The multiple organ dysfunction syndrome. *Dis Mon* 55(8):476–526, 2009.

the bedside as MODS, SOFA, LODS, or Denver, but it reliably predicts both outcome and resource utilization, has been refined to its current version, APACHE IV, and may be useful for benchmarking ICU performance [15].

EPIDEMIOLOGY

Incidence of MODS varies based on primary diagnosis and the scoring system used to determine organ dysfunction. Seventy-one percent of ICU patients have some organ dysfunction [16] and about half have MODS [17], depending on the criteria used. For example, in one adult trauma ICU 47% had MODS, defined by SOFA ≤3 in two or more systems [18]. Septic patients are more likely to have organ dysfunction and more organ failures than nonseptic patients and mortality is higher if sepsis is present (31% vs. 21%) [16].

ETIOLOGY

MODS is most often the result of shock, sepsis, and trauma but there are many causes (Table 160.2) [19]. Forty-one percent of those patients with organ dysfunction have sepsis [16]. Sepsis most commonly originates in the lung (68%) and abdomen (22%) but there are many causes of sepsis-induced MODS [16].

MECHANISMS OF MULTIORGAN DYSFUNCTION SYNDROME

The systemic inflammatory response syndrome (SIRS) is frequently viewed as a predecessor to MODS and these syndromes represent a continuum of dysfunction. Components of the SIRS response are seen in virtually all patients following operation or injury. This response is usually self-regulating and rarely progresses to MODS. MODS may be viewed as a result of an ongoing and dysregulated SIRS response with progressive organ system derangement.

Despite extensive efforts, the pathophysiology of MODS is not fully understood and remains an area of intensive investigation [20]. Several mechanisms for the onset and propagation of MODS have been proposed, including an initial insult leading immediately to organ failure, a "two hit" model, where an initial stimulus primes the immune system to respond to a subsequent insult with an exuberant reaction, and the concept that a continuous ongoing insult contributes to MODS [20]. In clinical practice, each of these scenarios may result in MODS.

A common theme in the onset and propagation of MODS is the presence of a disordered immune response. It is likely that ongoing tissue hypoxia leads to activation of the acute inflammatory response and to dysregulation of the immune system [21]. Although the inflammatory response is an important component of normal recovery from injury and illness, organ failure appears to result from a loss of the balance between the pro- and anti-inflammatory cascades [22]. The proinflammatory response to a stimulus predominates initially, with increased release of proinflammatory mediators, increased capillary permeability, macrophage and neutrophil activation with tissue invasion and damage, disordered apoptosis, and microvascular thrombosis [23]. This initial response is normally tempered by the anti-inflammatory response, but this relationship may become dysfunctional. Together, these processes lead to early onset of MODS. If the organism survives the initial insult and onset of MODS, a period of immunosuppression follows. During this period, the patient becomes highly susceptible to nosocomial infection, with a normally survivable event such as pneumonia representing a life-threatening "second hit" [24].

TABLE 160.2

RISK FACTORS FOR MODS

- Infection
  - Peritonitis and intra-abdominal infection
  - Pneumonia
  - Necrotizing soft tissue infections
  - Tropical infections (e.g., falciparum malaria, typhoid fever, dengue fever)
- Inflammation
  - Pancreatitis
- Ischemia
  - Ruptured aortic aneurysm
  - Hemorrhagic shock
  - Mesenteric ischemia
- Immune reactions
  - Autoimmune disease
  - Reactive hemophagocytic syndrome
  - Antiphospholipid antibody syndrome
  - Transplant rejection
  - Graft versus host disease
- Iatrogenic causes
  - Delayed or missed injury
  - Blood transfusion
  - Injurious mechanical ventilation
  - Treatment associated increased intra-abdominal pressure
- Intoxication
  - Drug reactions (anticonvulsants, carboplatin, antiretrovirals, colchicines, propofol, amiodarone, monoclonal antibodies)
  - Arsenic
  - Drug intoxication (ecstasy, cocaine, salicylates, acetaminophen)
- Endocrine
  - Adrenal crisis
  - Pheochromocytoma
  - Thyroid storm
  - Myxedema coma

Reproduced from Mizock BA: The multiple organ dysfunction syndrome. *Dis Mon* 55(8):476–526, 2009.

Extensive research continues to examine the potential role of the intestine in the onset and propagation of SIRS and MODS. From this work, it is hypothesized that acute injury damages the intestinal mucosa, leading to increased cytokine production from the intestinal epithelium and lamina propria with resultant systemic inflammatory response, and organ injury [25,26]. Under these circumstances, the intestinal barrier fails, leading to organ dysfunction. More recent studies have begun to examine the gut as a source of mediators that directly lead to organ damage [27]. These studies suggest that substances in the gut-derived mesenteric lymph directly lead to pulmonary dysfunction during shock states [28]. Full characterization of these mediators remains elusive.

CURRENT MANAGEMENT STRATEGIES

Course of MODS

Outcome in MODS partly depends upon host factors including genetics. Some patients are genetically predisposed to enhanced immune reactivity [29]. In most patients, MODS progression follows a typical sequence first described by Don Fry in 1980, beginning with lung failure, followed by the liver, gastric mucosa, and kidney [30]. Lung dysfunction was recently reaffirmed as the initial manifestation of MODS in the majority of patients [31]. Although a typical sequence of organ dysfunction usually occurs, the timing and rate of progression vary. MODS follows a bimodal onset with early and late MODS characterized by different patient characteristics and mechanisms of death [32]. An important distinction must also be made with early organ dysfunction during resuscitation, which is often reversible, and not necessarily the same as early MODS [33].

Respiratory organ dysfunction is the most common early manifestation of MODS but is often not associated with death [34]. Renal, central nervous and hematologic system impairments characterize MODS progression and are more strongly associated with mortality. Treatment of MODS therefore is focused on early recognition of those at risk, removing the source, and preventing MODS progression [35]. Clinicians should move briskly to optimize cardiorespiratory function, remove catabolic foci, and provide nutrition while using antimicrobials selectively and avoiding transfusion. Key advances in the treatment of patients with severe critical illness and MODS based on randomized controlled trials are summarized in Table 160.3.

TABLE 160.3

ADVANCES IN MANAGEMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROME BASED ON RANDOMIZED CONTROLLED CLINICAL TRIALS

Advance	Reference	Remarks
Early goal-directed therapy using venous oxygen saturation as a target.	[35]	Included as one of the Surviving Sepsis Guidelines.
Digestive tract or oropharynx decontamination with antimicrobials reduces 28-day mortality in ICU patients	[40]	Not widely practiced in the United States, as it conflicts with principles of antimicrobial stewardship
Lung protective ventilation strategies are associated with reduced mortality and increased ventilator-free days	[43]	Lung protective strategies are commonly utilized in ICU settings
Aggressive enteral nutrition is associated with improved immune function and less mortality in burned children	[49]	Landmark study suggested that protein repletion is essential in critically ill patients
Adjuvant treatment of patients with severe sepsis and septic shock with selenium is associated with decreased mortality	[53]	Mechanism of effect is unknown

Resuscitation

The Surviving Sepsis Guidelines summarize current best practice regarding resuscitation as of 2008 [36]. One major strategy to reduce MODS is to ensure optimal initial resuscitation. Resuscitation should target adequate oxygen delivery evidenced by oxygen saturation in mixed venous blood (SvO_2-saturation in mixed venous blood obtained from a pulmonary artery catheter or $ScvO_2$-saturation in central venous blood obtained from a central venous catheter in superior vena cava). Rivers et al. showed that by using oxygen delivery as a target for resuscitation with fluid, blood, and inotropes, lactic acidemia was less severe and outcomes were improved [37]. Inadequate initial resuscitation contributes to MODS [38]. For a comprehensive discussion of this topic, see Chapter 159.

Preventing MODS Progression

Source control is critical to prevent perpetuation of the inflammatory response [36]. Antimicrobials should be used as above, with tailored therapy and de-escalation [13]. On the basis of the possible role of the gut and enteric bacteria as a "motor" for MODS, several groups have proposed cleansing the bowel of bacteria to disrupt this relationship, but studies have yielded conflicting results and this practice remains controversial [27–29,39]. Although a recent European study supports parenteral and topical oropharyngeal antibiotics in reducing mortality, this is not widely accepted in the United States because it seemingly goes against the principle of antimicrobial stewardship [40]. Transfusion is a risk factor for MODS, suggesting that a conservative approach to blood transfusion is appropriate [41].

Mechanical ventilation contributes to distant organ dysfunction in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [42]. In the ARDSNet trial, the "lung protective strategy" of plateau ≤ 30 cm H_2O and tidal volumes ≤ 6 mL per kg body weight was associated with a reduction in all cause mortality of 9% compared with conventional ventilation with plateau pressures ≤ 50 cm H_2O and tidal volumes ≤ 12 mL per kg body weight [43]. A European study affirmed that use of a ventilation strategy with volumes greater than ARDSNet (>7.4 mL tidal volume per kg body weight) increased mortality [44]. For a comprehensive discussion of this topic, see Chapters 47 and 58.

Although Van den Berghe initially reported reduced mortality with intensive insulin therapy and the mortality reduction was in septic MODS [45], unacceptably high rates of hypoglycemia have since been reported [46] without a mortality benefit.

Steroid therapy in patients with sepsis and MODS may be used for select indications. For a comprehensive discussion of this topic, see Chapter 159.

Nutrition

There are data to suggest that early initiation of enteral nutrition improves outcome in patients with severe trauma, surgery, sepsis, and MODS. MODS is attenuated in patients receiving enteral nutrition within 24 hours as opposed to initiation later [47,48]. Recent retrospective data support early enteral feeding to reduce ICU and hospital mortality [49]. Both the American and European Societies of Parenteral and Enteral Nutrition (ASPEN and ESPEN) recommend enteral nutrition in ventilated patients if hemodynamics are adequate and gastrointestinal function is present and the gut works [50,51]. Arginine has been shown to be beneficial in surgical and trauma patients but cannot be recommended in septic medical patients because of immunoinflammatory characteristics [50]. However, omega fatty acids do appear beneficial in shortening length of stay, ventilator days, and mortality in septic patients. Serum selenium is depleted in trauma and surgical patients and some evidence suggests that selenium depletion contributes to MODS. Selenium repletion reduced MODS in a multi-institutional prospective randomized trial [52]. For a comprehensive discussion of this topic, see Chapters 159 and 192.

Recombinant human activated protein C was initially shown to reduce mortality in septic patients though its benefit has been questioned in recent studies [13]. rhAPC remains indicated in adults with high risk of death [36]. For a comprehensive discussion of this topic, see Chapter 159.

Continuous renal replacement therapy has been associated with reduction of MODS severity, theoretically due to modulation of elevated pro- and anti-inflammatory cytokines [53], but no large studies currently support its use for this purpose. Other novel therapies include pharmacologic manipulation of the microcirculation or augmentation of mitochondrial oxidative metabolism to enhance oxygen delivery [13].

PROGNOSIS AND ICU LENGTH OF STAY

Up to 20% of patients admitted to intensive care units develop aspects of MODS, with significantly increased morbidity and mortality [54]. MODS severity is decreasing but ICU mortality remains stable, perhaps because overall acuity is increasing [35,55]. In an epidemiologic study of sepsis in 2001, Angus determined that dysfunction of one, two, or three organ systems conveys 1%, 4.7%, and 20.7% mortality, respectively [19]. Four-organ dysfunction was associated with 65% to 74% mortality [16,19]. A more recent study examining the outcomes of critically ill patients reported ICU mortality of 10% for failure of three systems or less, increasing to 25% and 50% for four- and five-organ system failure, respectively. Mortality of seven-system failure was 100% [56]. In addition to mortality, MODS also affects long-term functional outcome [18].

MODS is the most common reason for prolonged stays in the intensive care unit, exceeding single organ system failure and simply the need for ventilatory support [54]. The onset of MODS is associated with a markedly increased length of ICU stay and risk of mortality [17]. Determining prognosis for individual patients with MODS remains challenging. Severity of organ dysfunction at the time of ICU admission or during the ICU stay correlates well with mortality, with the highest scores suggestive of a nonsurvivable situation, but does not allow accurate bedside prediction of an individual patient's outcome [7]. The strongest independent risk factors for death appear to be CNS failure (RR = 16.06) and cardiovascular failure (RR = 11.83) [56].

CONCLUSIONS

MODS is largely a result of medical progress and modern ICU care. A common denominator in the pathogenesis of MODS appears to be cellular hypoperfusion, leading to an imbalanced immune response, with resultant organ damage and failure. Treatment of patients at risk for MODS is supportive, ensuring adequate resuscitation, nutrition, source control, and support of individual organ systems as they fail. Despite modern critical care, MODS remains a common cause of death in critically ill patients.

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CHAPTER 161 ■ TRAUMA SYSTEMS

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INTRODUCTION

The number of people who die from injuries worldwide is tremendous, numbering in the millions annually. Trauma also constitutes a public health crisis in the United States and is responsible for 150,000 lives lost annually. Trauma is the fifth leading cause of death in the United States by 2006 statistics published by the Center for Disease Control (CDC). It is the leading cause of death in the young, ages 1 to 44. Trauma is responsible for more years of productive life lost than cancer and heart disease combined. On average 36 life years (productive years) are lost per one trauma death compared with 12 life years lost for a heart disease death and 16 life years for cancer. For every death from trauma, there are three individuals who suffer permanent disability and 75 who suffer temporary disability. The cost of injuries in terms of lost wages, direct and indirect medical expenses, and property damage is over $400 billion [1,2].

BACKGROUND

Trauma is a time-sensitive disease, perhaps more so than any other. Indeed, half of all injury deaths occur before any intervention. Patients who are bleeding have only minutes to live unless the hemorrhage can be controlled. This control often involves operative intervention. This time-sensitive nature is best described by the "Golden Hour" concept. Severely injured trauma patients have a "golden hour" during which they should be transported to a trauma center and their injuries addressed.

Baron Dominique Jean Larrey, Napoleon's surgeon-in-chief, created the concept of the flying ambulance or "ambulance volantes." The important concept was that soldiers injured on the battlefield should be treated in the field and evacuated for surgical treatment as soon as possible. To achieve this goal, Larrey instituted the use of a horse-drawn cart on the battlefield—the flying ambulance.

Trauma systems today are focused on the rapid transport of injured patients to the appropriate level of care. This should be a verified trauma center rather than simply the closest hospital with an emergency department. The goal of trauma systems is quite simple: get the right patient to the right facility at the right time. Delay in care may result in early effects such as hemorrhagic shock or late effects such as sepsis from open fractures.

DEFINITIONS

Typically, trauma patients are individuals suffering from penetrating, blunt, or thermal trauma. Clearly combinations of mechanisms may occur, as well as special circumstances such as blast injury. Trauma patients should be triaged to the most appropriate facility for care. Triage should be based both on severity of injuries identified as well as on risk of severe injury. This is because the total sum of injuries is not known until the patient has been fully evaluated at the appropriate trauma center. Just because a patient is hemodynamically normal at a given point in time does not imply that he or she will remain that way.

Trauma centers are hospitals that have been designated by the state or other designating authority as qualified to care for injured patients. There are usually a limited number of trauma centers in a certain geographic area so that each receives an adequate volume of patients required to maintain clinical expertise. Most frequently, trauma centers are designated as Level I through Level IV (some states have also designated Level V trauma centers). Level I trauma centers provide the highest level of care, plus have research and teaching responsibilities. Level II trauma centers are intended to also provide for the full spectrum of trauma care, but do not have the research and teaching requirements. Level III facilities do not provide the full spectrum of trauma care; they usually do not provide neurosurgical services. Level IV trauma centers provide trauma care commensurate with their existing resources.

HISTORY

In 1966, the National Academy of Sciences and the National Research Council published "Accidental Death and Disability: The Neglected Disease of Modern Society," which highlighted trauma as a major public health problem and made specific recommendations to reduce accidental death and disability. This led to national and state legislation including the Highway Safety Act and the National Traffic and Motor Vehicle Safety Act that was the first effort to regulate traffic safety and reduce automobile related death and injuries. The Emergency Medical Systems (EMS) program was also established. Later, in 1973, the EMS Systems Act identified trauma systems as one of 15 essential components of an EMS system and appropriated federal funds [3].

VERIFICATION AND DESIGNATION

The trauma system encompasses the complete care of the injured patient from the point of injury prehospital to the completion of the rehabilitative process. Important activities of that system include injury prevention, education, research, and financial viability. For this, there needs to be a lead agency established by each state that has the authority to create and execute policy for the injured patients, as well as designate the trauma centers to manage the injured patients. In order to receive a designation, a hospital or medical center has to demonstrate the standards of care established by the designating authority to achieve the level of trauma center, I, II, III, or IV desired. The trauma center is then evaluated and verified by either an internal team or an external reviewer, such as the American

College of Surgeons (ACS), as meeting the necessary criteria to be a trauma center in the system. This verification is then recommended to the lead agency of the state for designation of a trauma center. The lead agency regulates the quality of trauma systems components and establishes trauma triage guidelines.

The American College of Surgeons Committee on Trauma wrote the "Optimal Hospital Resources for Care of the Seriously Injured" in 1976 and there is presently the fifth edition called the Resources for Optimal Care of the Injured Patient 2006. The ACS established this document and his since added greatly to it as a resource for quality of care and standards of both trauma centers and trauma systems. The ACS verification process consists of hospital site reviews to determine quality of care and appropriateness of the trauma PI process. This verification process can then be accepted by the state as the designating authority to either designate or maintain designation of the trauma center. The ACS-COT also reviews statewide trauma systems to make recommendations to the system as a whole [4–8].

QUALITY OF CARE

Early studies, such as those done in Orange County and San Diego County, California, refined the preventable mortality concept. These studies were able to clearly identify a group of trauma patients that died from inadequate care—preventable mortalities. This concept provided a tool that could be used to examine quality of trauma care in any region or system. Teaching local and state legislators about the shortcomings of existing systems of care resulted in improved funding for trauma system components in many of the areas examined. Publication of these studies provided a necessary stimulus to many parts of the United States to begin to improve trauma care and develop trauma care systems.

As it became appreciated that data was important for determining quality of care, trends, and preventable mortality, trauma registries became a required part of trauma center work. Aggregations of these hospital-based trauma registries then developed as a result of State-sponsored trauma registries and research-oriented databases (such as the Major Trauma Outcome Study). Being able to examine populations of trauma patients led to developing mathematical formulas calculating the probability of survival of an individual trauma patient and comparing quality of care at trauma centers based on patient survival.

In 1990, the U.S. federal government passed Federal Law 101–590, Title XII of Public Health Service Act, which provided for grants to states to develop statewide trauma care systems. One of the products developed during the time the program was active (1992 to 1995) was the Model Trauma Care System Plan. The MTCSP was written to be a guide for states to implement a trauma system. The grant funds were modest (approximately $5 million per year), but resulted in states developing legislation, designating trauma centers, and establishing state trauma offices and procedures. Unfortunately, this Health Resources and Services Administration program underwent rescission of program funds in 1995 and was closed. In 1998, the program was again appropriated for several years, as before. During this time, a new State trauma system template was developed based on the public health model. Benchmarks, indicators, and scores were included in this federal document to permit states to score their own progress in developing an inclusive statewide trauma system.

The ACS-COT also helped develop the prototype Advanced Trauma Life Support Course in Nebraska in 1978 [9]. The course was then adopted and managed by the College as one of the most successful educational programs for doctors worldwide. ATLS lays the groundwork for the initial assessment and resuscitation of the injured patient. Every physician and medical student and perhaps all healthcare workers are familiar with the principles of the ATLS approach to trauma patients. These are the primary survey with the concept of ABCDE, and the secondary survey. In the primary survey, A is for airway, B is for breathing, C is for circulation, D is for disability, and E is for exposure. The secondary survey is a head-to-toe physical exam as well as pertinent history. The concept of the primary survey is to identify life-threatening problems and begin treatment within 15 to 30 seconds. The remainder of the ATLS teaches diagnostic and life-saving interventions as well as emphasizing the need to transfer a seriously injured patient to a trauma center. ATLS has been introduced in over 50 countries worldwide.

The ACS-COT also has developed a trauma system consultation process that can be applied to states, multistate jurisdictions, and even single-county systems.

As one examines the challenges and successes of trauma systems over the past 25 years, it remains clear that all phases of care are equally important to the successful outcome desired. In the context of critical care, let us examine each phase of care.

A. Identification/recognition of incident: Should the system fail to identify that an injury has occurred, the patient may succumb before medical care can be started. This happens not infrequently in rural and remote parts of our country. Even if the patient is found and transported to an appropriate trauma center, the delay in care may result in sepsis from open fractures not cared for in a timely manner or organ failure from delay in resuscitation. Some locations in our nation are so remote that even when the injured patient is recognized immediately, it can take more than 24 hours for him or her to arrive in a definitive care facility. The risk for poor outcomes is the same in either case.
B. EMS care and transport: The prehospital care systems are extremely variable across the United States. These systems range from volunteer to fire-based to government-employed professionals to contracted professionals. Again, the timely and vigorous resuscitation required by trauma patients can tax even the most experienced crew. Indeed, what quality EMS providers do is provide intensive care in the prehospital setting. Inadequate or delayed resuscitation can have profound immediate and late effects, similar to those already mentioned. The single greatest cause of mortality among trauma patients is head injury. If the patient is not rapidly and adequately resuscitated, the brain may never recover from even minor insult. The most severe brain insults may be rapidly fatal, even near the most capable institutions. Some brain injury patients appear to be awake at first but then drop their GCS score dramatically. The most classic of these is the epidural hematoma—the "talk and die" injury. As the epidural hematoma increases in size, herniation will occur unless the intracranial blood is rapidly evacuated. This entity is a good test of system performance; the patient must quickly get to a trauma center where a neurosurgeon is rapidly available. If this is the case, this is a readily survivable injury. Otherwise, it will result in death or permanent disability. Head-injured patients are among the most demanding in intensive care medicine. Early surgical intervention is much preferred over long-term care.
C. Emergency Department (ED) care: Many clinicians feel that the battle is won or lost by the time the patient arrives in the trauma center ED. This is not correct. Again, inadequate or delayed resuscitation may contribute to a poor outcome. This may happen many ways: too slow a resuscitation may result in prolonged hypotension with potential for organ damage—the brain being particularly susceptible. Too slow

to the operating room for care of open fractures may result in infection and sepsis.

Conversely, overaggressive resuscitation in the face of some injuries such as brain injury or pulmonary contusion may also cause problems. In these cases, too much resuscitation fluid may result in unnecessary tissue edema. This will cause increased intracranial pressure and poor perfusion in the closed space of the skull. With the lungs, the leaky capillaries associated with pulmonary contusion will cause the contusion to blossom more than necessary, with potential for more difficulty in ventilating the patient and weaning him or her from the ventilator.

D. Operating room (OR) care: Prior to intensive care unit (ICU) admission, many trauma patients will have required operative intervention. Inadequate correction of coagulopathy during the operation may contribute to later difficulties in ICU care. More hemorrhage into the tissues may cause pressure problems in fascial compartments, ongoing hemorrhage in the abdomen or chest causing abdominal compartment syndrome or thoracic compartment syndrome. All these compartment syndromes can also be caused by inadequate fluid resuscitation. Tissue hypoxemia and injury with later swelling and edema can result in any of these compartment syndromes. A modern massive transfusion protocol is a must for each trauma center today.
E. ICU care: Each of the issues mentioned above may also occur in the ICU setting. Just because the patient is now in the ICU does not mean that preventable problems will not arise. The burden remains for each care provider involved in the care of an individual trauma patient to make sure that care is provided in a thoughtful, timely, and expert manner. Under- or over-resuscitation can still occur. Delay in identification of injuries, such as bowel injuries may result in sepsis. Inattention to the need to decompress the stomach of a trauma patient with a gastric tube may lead to aspiration and pneumonia. Inattention to a small "CT" pneumothorax may lead to a complete or even a tension pneumothorax, particularly in the face of positive pressure ventilation. Patients can die of a tension pneumothorax even in an ICU setting. Intravenous catheters placed in the field under less-than-ideal circumstances may be contaminated and lead to sepsis if not replaced in a timely manner. Other chapters in this section give detail for the care of shock, resuscitation, management of sepsis, multiple organ dysfunction syndrome, traumatic brain injury, spinal cord injury, thoracic and cardiac trauma, abdominal trauma, burn management, and orthopedic injuries.
F. Ward care after leaving the ICU—these critical care trauma patients will need close follow up on the trauma center wards. Often sepsis may occur on the floor and MOD syndrome as well. The physicians following these patients must be capable of early recognition of these problems and institute immediate therapy when such problems are recognized.
G. Rehabilitation: Though many think the rehabilitative process begins after leaving the hospital, it should begin on the first full hospital day. Patients need to be mobilized early, and physical and occupational therapy consults should be on the admission orders. All patients with even minor head injuries need cognitive testing and evaluation by speech therapists. Any patients with head or spinal cord injuries or with a cluster of serious injuries need a physical medicine and rehabilitation physician involved with their care early in their hospitalization. The discharge plan needs to be formulated early and the resources of the patient and families need to be understood so the maximum benefit of rehabilitation and recovery can be realized. Trauma patients may also have been injured while using drugs or alcohol. Some trauma patients may have suicidal or depressive motives related to their injuries. All seriously injured patients may suffer from posttraumatic stress. It is the obligation of the trauma service to address these issues and have social services, counselors, and psychiatric services as part of the team so that the patient has the opportunity for the best possible outcome.
H. Performance Improvement, Research, Education, and Injury Prevention: An essential mission of any trauma service is quality assurance of care and performance improvement (PI). Opportunities for improvement in patient care from specific events or trends in complications must be recognized, discussed, and acted upon to promote the quality of care of trauma patients and the function of the trauma team. It is essential that all trauma centers have a current, thorough trauma registry to record all the clinical information from every trauma patient. As part of the trauma system, this information needs to be shared with the state trauma registry and the National Trauma Data Bank at the ACS. The information obtained from the trauma center registry feeds an effective PI program. The information from the trauma registry as well as those registries of the state and the NTDB also promote research and injury prevention. It is essential for the trauma center to be involved in injury prevention. The knowledge of which injuries are prevalent in that region will direct the focus of the injury prevention program. Research activity is encouraged at all trauma centers but is essential for a level one center. Finally, ongoing educational programs of all care givers involved with trauma care, including prehospital and rehabilitative services as an essential duty of a trauma center, and the trauma system.
I. Special Considerations in Trauma Systems

DISASTER MANAGEMENT

Most disasters are major incidents such as plane crashes, explosions in chemical factories, natural disasters such as hurricanes, or results of war and terrorist activities such as the events of 9/11/2001. An effective trauma system should be primed to manage these disasters. To successfully manage a disaster with many victims, there needs to be preplanning and organization of resources. There needs to be training done within the trauma system, stockpiling of supplies, an effective communication and triage system, and a clear understanding of the resources of each hospital and trauma center in the area. Without a trauma system, the wrong facilities would end up with the wrong patients (i.e., a seriously injured patient to a small hospital). The trauma system needs to predefine the triage of patients of a disaster according to severity of injury and volume of patients. This planning needs to have the trauma centers and trauma medical directors involved as they are the experts in the management of trauma patients. The most important principle is triage of the most seriously injured to the higher level of care in the fastest amount of time, and to avoid overtriage of minor injuries to the major trauma center. Triage guidelines should include re-triage to the trauma facilities. In a wider scope, there needs to be disaster planning between neighboring trauma systems in the event the trauma centers in a system are also damaged or unable to manage the load of injured patients [10,11].

RURAL TRAUMA

The establishment of a trauma system is of even greater necessity in a rural environment to improve the outcomes of the injured patients. In 9 of the 10 categories of injury for both urban and rural hospitals, the mortality rate is higher in the rural facility, and it is double for motor vehicle crashes.

Most of the problems with rural trauma relate to the time to definitive care at a trauma center. There is increased discovery time, time for the prehospital personnel to get to the patient, transportation over great distances and hard terrain, and transfer to the highest level of medical center. To decrease the mortality and morbidity of these patients, the trauma system needs to be firmly established and designate and train lower level trauma centers in areas of sparse population, provide consistent training of the volunteer prehospital personnel, and establish effective communication and transport systems between the prehospital and level III and IV trauma centers as well as to the regional Level II or I trauma center [12].

The American College of Surgeons sponsors specific courses for training in both rural trauma and disaster management, the Rural Trauma Team Development Course (RTTDC), and the Disaster Management and Emergency Preparedness course (DMEP).

In summary, trauma systems provide for early recognition, prehospital care, resuscitation and operative care critical care management, long-term care, and rehabilitation. Performance improvement remains an essential trauma system function.

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CHAPTER 162 ■ TRAUMATIC BRAIN INJURY

TODD W. TRASK AND ARTHUR L. TRASK

When Dr. Rosner first published his recommendations that were to change the management of traumatic brain injury (TBI), he recommended using cerebral perfusion pressure (CPP = mean arterial pressure [MAP]—intracranial pressure [ICP]) as a better way to manage severe TBI patients than just using the level of ICP [1,2]. This was the beginning of the changes in TBI management. Dr. Marion and Spiegel have published the article "Changes in the Management of Severe TBI: 1991–1997" [3]. Recommendations to change severe TBI management, based on evidence, developed by The Brain Trauma Foundation, in combination with the Trauma committee of the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and AANS/CNS Joint Section on Neurotrauma & Critical Care have been updated several times with the latest version in 2007 [4]. Neurosurgeons were surveyed by the Brain Trauma Foundation in 1991 and 1997 to determine if they were changing their management of severe TBI patients. The use of steroids was significantly reduced from 1991 to 1997 and hyperventilation was also discontinued. In 2004, we published our results of an evidence-based medicine protocol [5]. Our results showed a decrease in hospital intensive care stay by 1.8 days ($p = 0.021$). The Glasgow Outcome Scores (GOS) of good or moderate from 1991 to 1995 were 43.3%. For the period 1997 to 2000, our patients' GOS of good or moderate were 61.5% ($p = < 0.001$). The overall mortality rate decreased from 17.8% for the early group compared to 13.8% for the later group [6–8].

We recommend that the intensive (ICU) care of severe TBI patients be driven by institutional protocols developed by key participants, that is, ICU care providers, using current recommendations for managing these patients [4]. Each hospital has different approaches to critical care and the reason we suggest assembling this key group of individuals is to assure that the plan for care fits into the way things are done in each hospital.

Above all, we recommend an evidence-based approach to the care of these critically ill patients. New evidence will be presented each year and adopting what has high credibility to that protocol makes good sense. We recommend keeping a TBI patient database to know with certainty how your results compare with other trauma centers in the USA and the world. By having a TBI database, you might also consider doing a prospective study using different techniques for similar TBI problems or management [9–13].

IDENTIFICATION

Identification of severe traumatic brain injury requires two criteria to be met. First, the Glasgow Coma Score (GCS) must

be 8 or less. The GCS was first described in 1974 by Graham Teasdale and Bryan J. Jennett, professors of neurosurgery at the University of Glasgow, Scotland. In 1981, they approached F.A. Davis, the author of a textbook *Management of Head Injuries* who included the scoring system for identification of different levels of TBI.

The next criteria for a severe TBI is an abnormal brain computed tomography (CT) with findings such as contusion, hematoma, diffuse axonal injury (DAI), compressed basal cistern, subarachnoid hemorrhage (SAH), and/or other clear signs of brain injury. When only an abnormal GCS is present, it is possible to be due to something other than TBI. When an injured patient arrives in an emergency department (ED), these two assessments are done to identify a severe TBI patient. When these criteria are met, the patient should be moved to a Neurotrauma ICU, a part of the recognized Trauma Center, as soon as possible, provided other types of operative treatment are not more urgently needed. Placement of an intracranial pressure monitor should be considered in the multiple-injured TBI patient, simultaneously with the non-neurosurgical operative procedures.

MONITORS

We recommend intracranial pressure (ICP) monitors for assessing the moment-to-moment status of your patient. Generally, a ventriculostomy type monitor is superior to an intraparenchymal (Bolt) monitor. The ventriculostomy can accurately determine the intracranial pressure but also allows the neurophysicians to drain cerebrospinal fluid (CSF). The latest recommendation for ICP monitors is to have an electronic continuous record with instantaneous alerts for significant increases to allow immediate interventions per protocol. Many devices are available for measuring brain oxygen levels as well as oxygen from the jugular bulb. The value of these measurements is yet to be determined by the BTF and AANS [14–19].

An understanding of the Monro-Kellie doctrine is essential. In 1783, Alexander Monro deduced that the cranium was a "rigid box" filled with a "nearly incompressible brain" and that its total volume tends to remain constant. The doctrine states that any increase in the volume of the cranial contents (e.g., brain, blood, or cerebrospinal fluid), will elevate intracranial pressure. Furthermore, if one of these three elements increases in volume, it must occur at the expense of the volume of the other two elements. In 1824, George Kellie confirmed many of Monro's early observations. If as a result of trauma a hematoma forms on the outside of the brain (epidural hematoma), under the dura (subdural hematoma), or within the brain itself, the space occupied by the hematoma must result in a commensurate decrease of the intracranial blood or CSF volume. Once these compensatory mechanisms are exhausted, intracranial pressure will rise rapidly, and brain herniation may occur. Cerebral edema can mimic an expanding mass lesion, with similar pathophysiology, and potential for the irreversible damage associated with uncal and/or tonsillar herniation (see graph in Fig. 162.1).

In general, the reaction to an intracranial mass or cerebral edema is to reduce the amount of venous blood and CSF within the skull. The body's response to the injury is to keep the pressure inside the skull as close to normal as possible by reducing those volumes that can be reduced. When a sudden increase of ICP occurs and the patient has a ventriculostomy, the neurointensivist may drain additional CSF from this closed box. This in turn helps to keep the ICP under control while other measures are taken to reduce the ICP in a more lasting fashion. We will discuss more about this under patient management.

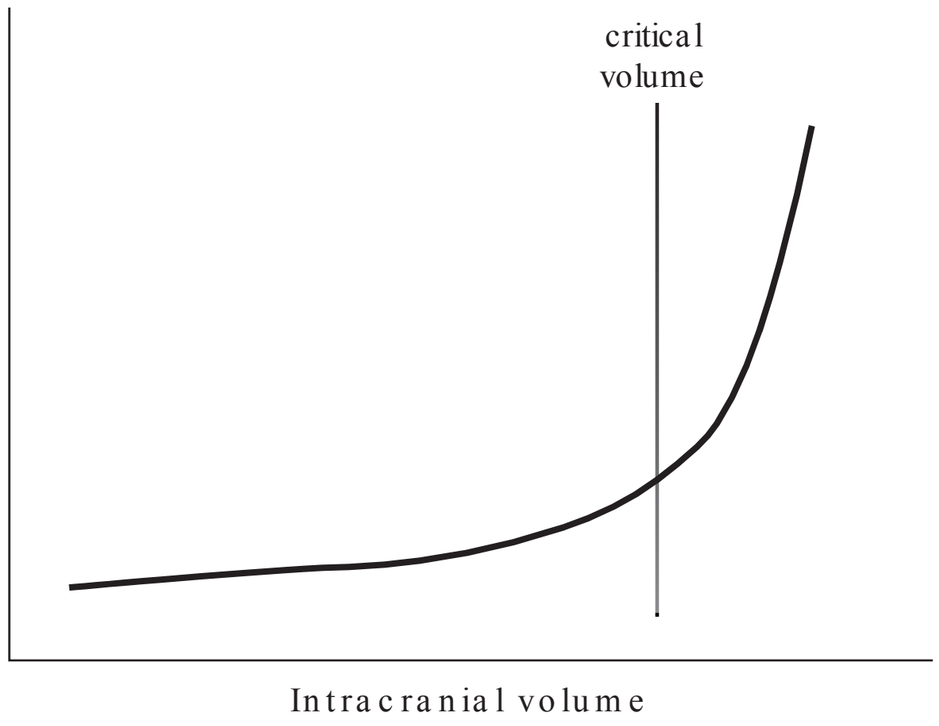

FIGURE 162.1. As the Monro-Kellie doctrine indicates, the skull is a closed box. When intracranial volume increases to the *critical volume* due to traumatic brain injury, that is, subdural hematoma (SDH), epidural hematoma (EDH), or massive cerebral edema, note the dramatic vertical increase in intracranial pressure. If this occurs and the volume is not reduced, brain herniation will occur.

The next consideration for the severe TBI patient is determining what other injuries the patient might have. A qualified trauma surgeon must be involved to assist the neurointensivist with the fluid/blood product management. For example, a patient with a class III anterior posterior pelvic fracture will lose huge amounts of blood even if managed by a trauma orthopedist with pelvic circumference reduction. This is an indication for a pulmonary artery catheter (PAC) (or one of the newer devices for monitoring pressures and cardiac output) to monitor the resuscitation as closely as possible. The goal is maintaining the patient's systolic pressure at or above 90 torr. In the book, *Management and Prognosis of Severe Traumatic Brain Injury*, a joint project of the Brain Trauma Foundation and American Association of Neurological Surgeons, class two evidence states that allowing the systolic BP to drop below 90 torr will likely produce secondary brain injury. The BTF class two evidence criteria are clinical studies in which the data was collected prospectively or retrospective analyses that were based on clearly reliable data. Types of studies so classified include: observational studies, cohort studies, prevalence studies, and case control studies. Class two evidence shows that post injury hypotension has dramatic impact on the brain injury outcome. We recommend using the PAC data to assist in fluid/blood product management to maintain a PCWP between 10 to 15 mm Hg and a CI of 2.6 L per minute per m^2. Invasive hemodynamic monitoring may also help avoid fluid overload and possibly associated increases in cerebral edema. A new monitoring device is now being evaluated for these multiply-injured patients. The use of The InSpectra^{TM} StO_2 Tissue Oxygenation Monitor will provide continuous, real-time information for perfusion status monitoring and a new hemodynamic parameter (StO_2) to assist clinicians in the early detection of inadequate tissue perfusion (hypoperfusion). This device would noninvasively monitor hemodynamic status and tissue oxygenation, both of which are critical for severe TBI patients [19].

The oxygen saturation level and the PCO_2 level are also extremely important for the ICU management of these patients. The Brain Trauma Foundation has gone to great lengths to provide training to prehospital providers so that they recognize the importance of keeping the O_2 saturation more than 90%. This same standard must be maintained in the ICU as well. Patients with severe TBI should have endotracheal intubation as early as possible after the traumatic event. Once the patient arrives in

the Trauma Bay, the ventilator must be set to assure adequate oxygenation and also to maintain the PCO_2 level around 38 to 40 mm Hg. Most intensivists/respiratory care physicians recommend keeping the head of the bed elevated to 30°. In addition to aiding respiratory function, elevation also provides some slight assistance in maintaining the ICP in the desired range.

Major trauma accompanied with significant blood loss often will result in coagulopathy. The American College of Surgeons Committee on Trauma in their Advanced Trauma Life Support Course™ classifies shock into four classes. Primarily, class III (1,500 to 2,000 mL blood loss) and class IV (> 2,000 mL blood loss) are frequently associated with coagulopathy. In addition, we also know that certain severe TBI cases may present or develop coagulation abnormalities. Using a device called a Thromboelastogram™ (TEG) will assess the coagulation status of these patients and offers a rapid technique for identification of coagulation problems. A TEG is also useful for identifying hypercoagulability, and the associated risk of venous thromboembolism [20–26]. Electroencephalography (EEG) monitoring and Ultrasound monitors are being used more frequently today and are very useful for those patients being treated with pharmacological coma.

It is necessary to observe closely for impending Diabetes Insipidus (DI) by frequent serum Na determinations, urine output > 200 cc per hour and urine specific gravity < 1.005. This is considered Central DI and is due to a lack or an inadequate amount of ADH (vasopressin). Treatment is with subcutaneous vasopressin (ADH) or intravenous deamino-8-d-arginine (DDAVP).

Cerebral microdialysis is possible with a ventriculostomy in place. During periods of metabolic stress with TBI, many neurointensivists are using this technique to measure changes in lactate, excitatory amino acids, glycerol, glucose, and pyruvate as well as other metabolic compounds during periods of metabolic stress of TBI. The future of patient management may be augmented by these studies, but at present no recommendations are evidence based.

PATIENT MANAGEMENT

Avoiding seizures is a key management endeavor. This activity may exacerbate metabolic derangements already present, and result in secondary injury. Loading severe TBI patients with phenytoin is recommended provided adequate hemodynamic stability exists. The loading dose we recommend is 18 mg per kg at a rate of 25 mg per minute. The maintenance dose is 100 mg every 8 hours IV. Maintenance dosing for 7 days is indicated. Class II evidence shows that prophylactic anticonvulsants have no benefit after 7 days, provided there have been no seizures. We recommend obtaining a free phenytoin level 72 hours after the loading dose [27–29].

The syndrome of inappropriate antidiuretic hormone (SIADH) may occur. This usually appears late in the course of TBI and appears as hyponatremia since the hormone causes water retention diluting the plasma electrolytes. If early in the care for mild hyponatremia, water restriction is usually sufficient but, the CPP should not be allowed to drop as a result of the restriction. This syndrome needs to be distinguished from the cerebral salt wasting syndrome which is thought to be caused by a brain-secreted natriuretic peptide. The difference can usually be elicited by measuring urine sodium levels that are inappropriately elevated in cerebral salt-wasting syndrome. Treatment for this syndrome is salt and volume replacement. For an in-depth discussion of this subject, readers are referred to Chapter 72.

Attempting to keep the brain activity at a minimum is another management activity. Fast acting drugs are suggested during the first 48 hours after injury to allow the neurospecialists to reexamine the patient frequently to determine deterioration or improvements in coma scoring. Use of propofol and fentanyl for this period is suggested. When the status of the patient has been well established, we suggest switching to longer acting (less expensive) medications. We recommend using lorazepam and morphine to keep the Richmond Agitation Sedation Scale (RASS) score @ −2 to −3 (see Fig. 162.2). The RASS has been shown to be a useful adjunct in the management of the severe TBI patient [30].

Another adjunct in the management is temperature control. While a study has been suggested using hypothermia (to 32°C) for patients aged less than 45 years, normovolemia and with a GCS > 4, the multicenter trial did not confirm this hypothesis and was terminated [31]. Nonetheless, it is essential to avoid temperature elevations. Anticipating temperature elevations and monitoring closely will allow the management team to use cooling techniques and/or medications such as acetaminophen to keep the temperature ≤ 38°C.

Gastric mucosal protection is necessary to prevent stress ulcers. We suggest prophylaxis using a histamine receptor antagonist, a proton pump inhibitor. Once a feeding program is started the problem of stress ulcers decreases.

The nursing staff must play an important role in the management of these critical ill patients. They should repeat the motor score and eye score to detect improvement or deterioration. They must assume responsibility for frequent checks of urine output, temperature, ICP, CPP, Hb, electrolytes, and graphing trends for the neurointensivist to review during reexaminations.

When the nurse documents an elevated ICP of ≥ 20 for more than 10 minutes, (these are suggested criteria and each hospital will need to decide what early criteria they will use) we suggest immediate drainage of CSF by the ventriculostomy. Next optimize temperature control, increase sedation, and paralyze patient. The next step is again a decision each hospital should make. Hyperosmolar therapy with mannitol or hypertonic saline should be considered. Nicole Forster in her publication suggests that mannitol is the first choice for pharmacological ICP reduction [31]. Cruz, Battison, Valadka, Shackford, Ware, and White all believe some form of hypertonic saline should be used to reduce the ICP [32–38]. There are considerable differences of opinion on this topic. At this time, each facility should review these articles and the ICU team must decide on what hyperosmolar therapy to use. Repeat imaging should always be considered in the event of unexpected ICP changes.

If the ICP rises to ≥ 25 for 30 minutes the neurology team should discuss the use of pentobarbital coma or consider performing an early decompressive craniectomy as recent literature suggests a role for this procedure in some patients [39–42]. The best results are observed when the craniectomy is performed early and before significant deterioration has occurred.

Hopefully, with all of the above strategies, patients will gradually improve showing better motor scores and improved CT scan. The criteria for discontinuing the major TBI protocol should be (a) when the patient is requiring less sedation with the RASS being −2 to −3, (b) the paralytics have been discontinued, (c) temperature control is no longer a problem, (d) recent CT scan shows stability and/or improvement, and (e) the ICP has been ≤ 20 for at least 24 hours and the neurosurgeon has discontinued the ventriculostomy.

During this critical period, nutritional support should be initiated. Assessment of the metabolic needs of these patients is crucial and nutritional support plays a major role in recovery. A consultation with a physiatrist, who in collaboration with the neurointensivist team, will suggest the physical therapy, occupational therapy, and speech therapy. These therapies will be started to aid in the long-term recovery of these patients.

Score	Term	Description
+4	Combative	Overly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive, vigorous
0	Alert & calm	
−1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to voice (≥10 sec)
−2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)
−3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated. (score 0 to +4)
2. If not alert, state patient's name and say to open eyes and look at speaker
   b. Patient awakens with sustained eye opening and eye contact. (score −1)
   c. Patient awakens with eye opening and eye contact, but not eye contact. (score −2)
   d. Patient has any movement in response to voice but no eye contact. (score −3)
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation (score −4)
   f. Patient has no response to any stimulation (score −5)

FIGURE 162.2. The Richmond Agitation Sedation Scale (RASS). [Adapted from Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 166:1338–1344, 2002.]

FUTURE POTENTIAL TREATMENT OPTIONS

a. A multicenter trial: Citicoline Brain Injury Treatment Trial (COBRIT). This is a phase 3 double-blind, randomized, prospective clinical trial to determine if treating head injured patients (severe, moderate, and complicated mild) with citicoline will improve recovery. Citicoline, also known as cytidine diphosphate-choline (CDP-choline) is a psychostimulant/nootropic. It is an intermediate stage in the generation of phosphatidylcholine from choline and increases dopamine receptor densities. The patients are randomized to citicoline or placebo. The reason for this compound being tested is that several meta-analyses indicate a benefit of this compound in stroke and dementia. Eight sites are participating.
b. Spreading Depressions (formerly COSBID) is in the study preparation phase. Cortical Spreading Depression (CSD) is a wave of mass neuronal firing, neuronal, and glial depolarization. It propagates through gray matter at a rate of between 1 and 5 mm per minute and depletes energy stores and may activate cell death cascades. Spreading Depressions (SD) are seizure like waves that actively propagate a breakdown of ion homeostasis and may alter blood flow through injured, but potentially salvageable brain tissue. The objective of this study will be to determine if SD actually causes secondary brain injury after TBI. If the answer is yes, then a method to block the SD waves will be developed. The results of this study are eagerly awaited.
c. Another study, labeled SOLVAY, is designed to study SLV334 in a phase 2a randomized, placebo-controlled, double-blind pharmacokinetic and safety study. If shown to be safe, a phase 3 trial of this drug which has a new mechanism—endothelin antagonism, matrix metalloprotease inhibition, and "anti-apoptotic effect"—will be developed with multiple centers.
d. A phase 3 prospective randomized multicenter clinical trial is underway with an expectation of about 1,400 patients over a 5-year period. Titled the *B*rain *O*xygen and *O*utcome in *S*evere *T*raumatic Brain Injury (BOOST) Study, it is designed to compare the standard management of ICP/CPP versus brain oxygen-based therapy to determine which category of patients will have the best long-term outcome.

Much progress in treating TBI has occurred. Careful management of the CPP, ICP, cardiac output, tissue oxygenation, PCO_2, temperature, and the other body parameters that support brain metabolism and recovery is indicated. Much opportunity for improving the management of TBI patients still exists when given by well-trained critical care teams resulting in more updates on management sequelae in this ever-encouraging field of emergency trauma care.

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CHAPTER 163 ■ SPINAL CORD TRAUMA

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INTRODUCTION

"The Spine" is often thought of a single unit, as is "the liver" or "the intestines," but the concept is somewhat misleading. "The Spine" is really a structure with two parts. The first part, the bony spine, serves dually to support the body and to protect the vulnerable neurological structures inside. The second of the two parts of the spine, the neurological spine, is more than just a "coaxial cable" connecting the brain to the remainder of the body. The neurological spine, the spinal cord, is a complex extension of the central nervous system, capable of learning and adapting. When the bony protection fails, the spinal cord (and possibly the cervical-medullary brainstem or the cauda equina) is traumatized with multiple systemic consequences. These consequences may result in a catastrophic injury. To better develop treatments for spinal cord injury, the pathophysiology of the injury continues to be thoroughly studied [1–8]. In this chapter, traumatic forces are emphasized, but the reader should keep in mind that vascular, infectious, or toxic/metabolic/ischemic damage to the spinal cord may present in a patient with a similar profile of deficits and clinical challenges.

Injury to the spine can be thought of in two phases. The first phase called "Primary Injury" is the moment when excessive kinetic energy is transmitted to the spinal cord in the moment of trauma. The "Secondary Injury" follows immediately after that as the damage from the primary injury creates biologic sequelae. Secondary injury in spinal cord injury (SCI) is believed

to involve the release of neurotoxic chemicals, creation of free radicals, recruitment/activation of macrophages, disruption of the blood-spinal cord barrier, generation of lipid peroxidation, presence of oxidative cell stress, and other events [9]. Even without a complete understanding of all of the variety of events in spinal cord injury, it is believed that secondary injury can be modulated with appropriate therapeutic interventions. These include, but are not limited to, decompressive surgery [10,11] steroids [12–17], hypothermia [18–23], immunomodulation [24–26], nutrition [27,28], and other therapies.

Given the tremendous socioeconomic and psychosocial impact of spinal cord injury, there have been several human clinical trials [12,15,29–32] to date in an effort to limit the secondary injury, but there is no one therapeutic strategy that is clearly effective in affecting outcome.

Surgical management of spinal cord injury is also still under debate, especially in terms of the timing and utility of the surgical intervention [11,33,34]. Fortunately, there are treatments available for the spinal cord injured patients such as physical therapy, outpatient therapy, and adaptive therapies [35–40].

The future of treatment for spinal cord injured patients will likely involve a combination of techniques, such as applying neurotrophic factors, nerve grafting, cellular injection, hypothermia, tissue engineering, neuromodulation, and other innovative approaches. This chapter addresses the many problems unique to the management of a spinal cord-injured patient. The specific surgical treatments for each pathologic entity are beyond the scope of this chapter.

HISTORY

The Edward Smith Papyrus [41–43] represents one of the earliest records of spinal cord injury. Dating back approximately to 2500 B.C.E., there is a case report by Imhotep, a physician and architect to the Pharoh Zoser III. In this Papyrus, he describes 48 trauma cases, 6 of which involve vertebral column injury. In the most famous case, Imhotep describes a case of "crushed vertebra" where "incontinence, paralysis, and loss of sensation" follow. In his medical opinion, treatment was not to be pursued. The Greek Physician Galen, some 3000 years later, conducted animal experiments noting the difference in effects between longitudinal and horizontal cord transactions [41]. Only 500 years after Galen, the laminectomy was introduced by Paulus. In 1543, Vesalius then introduced remarkably detailed anatomical drawings of human anatomy. In the early twentieth century, despite significant scientific and engineering advancements, the opinion of Imhotep still reigned true and traumatic SCI was felt to be a terminal condition.

The recognition that spinal cord injury should not be viewed as a terminal condition owes much to the insights of Sir Ludwig Guttmann (UK) and Sir George Bedbrook (Australia). In the aftermath of World War II, these two physicians were at the forefront of refusing to accept the inevitable prognosis for SCI [44,45]. They pioneered the idea that the sequelae of SCI do not need to be fatal and that an intensive regiment of physical therapy and care may be life-saving and life-improving.

EPIDEMIOLOGY

There are more than 200,000 people in the United States living with a chronic SCI. Each year, approximately 11,000 Americans are afflicted with this condition [46]. More than half of the people who sustain SCIs are 15 to 29 years old (CDC data: http://www.cdc.gov/ncipc/factsheets/scifacts.htm). Approximately 80% of the injured are male [46]. There is a growing trend of seeing SCI among middle-aged and elderly patients due to improved lifestyle habits and improved survivability of injuries. Data collected from North America, Europe, and Australia confirm similar results [47]. The cervical spine is the most commonly injured site, with the remaining injury sites divided between thoracic, thoracolumbar, and lumbosacral levels [48].

The mechanism of injury can be blunt (e.g., motor vehicle accident, fall, assault) or penetrating (e.g., gunshot wound, knife, and other sharp object). Approximately 50% of the injuries derive from a motor vehicle accident, with the remainder primarily from falls (23%), violence (14%), and sports (9%) [46].

NEUROLOGIC INJURY

As a trauma patient is assessed through the initial "ABCDE" of Advanced Trauma Life Support, the physician must perform a neurologic examination. The neurologic examination is of paramount importance localizing the probable site of injury as well as to assess the severity of injury to the spinal cord. Once the SCI is identified, the physician can classify the injury by mechanism (e.g., penetrating vs. blunt), level (cervical, thoracic, lumbar), and degree of neurological impairment (often through the American Spinal Injury Association [ASIA] scale).

To assess the degree of neurologic injury, particular attention is paid to the motor, sensory, reflex, and rectal examinations. Based on the degree of functional impairment, the ASIA has proposed an easily used scoring system (Table 163.1). The neurologic injury is categorized using this score and by noting lowest normal segmental level. (When referring to the "level" of injury, it is important to note that the level is the corresponding "neurological level" or dermatological level and not the "bony level." For example, consider a patient shot in the spine. A neurosurgeon evaluates the patient and states that the patient has a complete neurological injury at the "L4" level. This means that the lowest spinal level with completely normal function is at the L4 neurons of the spinal cord. The bony disruption, however, may be at approximately T12, which corresponds to the locations of neurons that innervate L5 and below.)

In this classification scheme, the severity of injury is denoted by Grade, followed by letters A-E. The letters serve as shorthand to classify the severity of injury as it relates to sensory and motor function. Grade A (complete) denotes a complete injury with no sensory or motor function preserved in sacral segments S4–5. Grade B (incomplete) denotes sensory, but not motor function preserved below the neurologic level and extends through sacral segments S4–5. Grade C (incomplete) denotes motor function preserved below the neurologic level with muscle strength graded below antigravity strength. Grade D (incomplete) denotes motor function preserved below neurologic level with muscle strength graded more than or equal to antigravity strength, but not normal. Grade E denotes a normal

TABLE 163.1

AMERICAN SPINAL INJURY ASSOCIATION GRADING SCALE FOR SPINAL CORD INJURY

Clinical grade	Neurologic examination
A	No motor or sensory function preserved
B	Sensory but no motor function preserved
C	Nonuseful motor function preserved (less than antigravity strength)
D	Motor function preserved but weak
E	Normal motor and sensory function

sensory and motor exam [49,50]. The grades have a prognostic feature. Complete recovery of function after a Grade A injury is unlikely. However, improvement of one or two grades is seen in more than 10% of patients. Some recovery is most likely to occur in Grade D injuries [51].

SCI may be also classified as complete or incomplete. In complete SCI, there is no preservation of motor function and/or sensation for three spinal segments below the level of injury. Complete injuries above T6 are usually associated with spinal shock. Spinal shock is characterized by: hypotension from interruption of sympathetics, bradycardia from unopposed vagal (parasympathetic) output, hypothermia, and transient loss of all neurologic function resulting in a flaccid paralysis and areflexia. Incomplete SCI may be further subclassified into specific neurological symptoms based on the anatomy of the injury.

SPECIFIC NEUROLOGIC SYNDROMES

Specific neurologic syndromes have been described for particular incomplete spinal cord injuries [52,53]. These syndromes include the anterior cord syndrome, the central cord syndrome, the posterior cord syndrome, Brown-Sequard (hemisection cord syndrome), conus medullaris syndrome, cauda equina syndrome, and cord concussion syndrome.

The **anterior cord syndrome** is characterized by complete paralysis and hypoalgesia (to pain and temperature) from damage to anterior and anterolateral column function below the level of injury, with preservation of proprioception (vibration and position sense) and light touch from posterior column function. This syndrome occurs most commonly after trauma focused at the anterior spinal cord as well as ischemia in the territory supplied by the anterior spinal artery, which supplies the corticospinal and spinothalamic tracts in the anterior 2/3 of the spinal cord. It is classified as an ASIA B injury.

The **central cord syndrome** is characterized by motor dysfunction more pronounced in the distal upper extremities than in the lower extremities ("man in a barrel"), accompanied by varying degrees of sensory loss and bladder dysfunction. The injury occurs characteristically after a hyperextension injury in elderly patients with acquired cervical stenosis from spondylosis or in athletes with congenital cervical stenosis. The injury can be seen in the absence of any clear radiographic disruption of the bones or ligaments. Most patients recover the ability to walk, with partial restoration of upper-extremity strength. It is associated with severe allodynia of the hands. (Allodynia is pain from stimuli that are not normally painful.)

The **posterior cord syndrome** is an uncommon presentation in which position sense, vibration sense, and crude touch are impaired due to injury to the dorsal columns or injury directed to the posterior of the spinal cord.

The **Brown-Sequard syndrome,** or **hemisection cord syndrome,** presents with ipsilateral paresis and loss of proprioception, touch, and vibration below the level of the lesion and the contralateral loss of pain and temperature sensation. This can be the result of penetrating injuries or asymmetrical lateral closed injuries resulting in a spinal cord hemisection, and is usually not seen in the pure form. Asymmetrical, lateral closed injuries are often confused with an ipsilateral brachial plexus injury.

The **conus medullaris syndrome** occurs with injuries at the thoracolumbar junction. This syndrome has components of both spinal cord and nerve root injury due to the dense population of nerve roots emerging from the caudal end of the spinal cord. Symmetric lower-extremity motor impairment and anesthesia with bowel, bladder, and sexual dysfunction are typically seen. There is typically a symmetric "saddle" area loss of sensory function. Spinal cord function recovery from this syndrome is less likely than recovery from nerve root injury. In cases of the **cauda equina syndrome,** partial recovery is possible with decompression [54]. Cauda equina injuries occur at spinal levels below the termination of the cord, typically at L1 or below.

Cord concussions present with transient neurologic symptoms followed by rapid resolution. These injuries are seen most commonly in athletes with low velocity hyperflexion or extension injuries of the cervical spine. Complete recovery is the rule; however, patients should be evaluated meticulously for severe stenosis or occult spinal instability and intraspinal hematomas. This is in contrast to "stingers or burners" that involve cervical nerve roots only. The issue of "return to play" [55–60] is especially important in the field of athletics. Currently, there is no agreed upon measure to predict which athletes are most at risk of further injury. However, "functional" stenosis [61] and anatomic measurements [56] may both play a role.

PATHOPHYSIOLOGY

The injury to the spinal column and spinal cord involves the transfer of energy sufficient to disrupt the cell membranes and mechanical attachments of the ligaments, muscles, and joints. This results from movement and stressing of the spine beyond its biomechanical/physiological limits in hyperflexion/hyperextension, rotation, compression, or a combination thereof. Injury may result in retropulsion of materials (e.g., bone, cartilage, blood, foreign body) into the spinal canal. Disruption of the vertebral column may also damage the spinal cord within the canal (e.g., dislocation injuries) by reducing the spinal column diameter and compressing the spinal cord. The spinal cord may also be injured by direct laceration or transaction of the cord (e.g., bullet or knife injury). Direct crush, stretch, and shear injury to neurons within the spinal cord leads to immediate cell death.

Secondary injury occurs as the body responds to the damage from the primary injury. There are many mechanisms that initiate secondary injury. These include systemic hypoxia (e.g., hypotension from neurogenic shock or hypovolemic shock, hypoperfusion, etc), local vascular insufficiency (local hypoxia) from trauma, direct penetrating trauma, and spinal compression.

The secondary injury involves biochemical changes and the release of neurotoxic substances. Toxic substances, such as glutamate and free radicals contribute to cell damage and death. These biochemical changes lead to excitotoxicity, neurotransmitter accumulation, arachidonic acid release, free radical production, eicosanoid production, and lipid peroxidation. There are electrolytic shifts such as increased intracellular calcium, increased extracellular potassium, and increased intracellular sodium. The disruption in electrolytes is compounded with the loss of energy metabolism, as the neurons are unable to produce adenosine triphosphate (ATP). Within minutes to hours, oxidative stress leads to cell necrosis. Apoptosis follows further depletion of cells. Over the following days to months, demyelination occurs with the loss of oligodendrocytes. Glial scar formation and axonal degeneration/retraction follow [9]. The damage of the cord may be visualized as edema.

Because spinal cord-injured patients frequently also suffer polytrauma, they are susceptible to derangements of homeostasis. Cardiovascular and pulmonary compromise may affect perfusion and oxygen delivery to the spinal cord, exacerbating the damage. Recent work in animal models of SCI suggests that SCI itself may further disrupt homeostasis. There is evidence from animal models of SCI for a systemic inflammatory response capable of disrupting the cardiopulmonary and renal system [62]. Vasoactive substances released by injured cells

and endothelin released from damaged capillaries may also disrupt the spinal cord microcirculation. Ischemia may thus cause neurologic deficits to extend rostrally beyond the initially injured area [63,64].

Because cell death due to secondary injury is an ongoing process, it is believed that early pharmacologic intervention and maintenance of adequate tissue perfusion can salvage these neurons. Given that only 5% to 10% of the descending pathways are necessary for retention of some neurological function [4], even a modest preservation of axons during an injury could have a profound impact on the life of a person with spinal cord injury.

ACUTE MANAGEMENT

Care of the spinal injury patient begins in the field with Emergency Medical Services personnel. The "ABCDE" (**A**irway, **B**reathing, **C**irculation, **D**isability, **E**xposure) of Advanced Trauma Life Support are followed. Attention to maintaining a patent airway and the management of shock take precedence. The patient is immobilized with a rigid cervical collar and backboard for transportation to a trauma center. Intubation and helmet removal should be attempted only with strict attention to maintaining neck alignment. This is particularly important in unresponsive patients, as 3% to 5% of comatose patients have a coexisting cervical spine injury. Additionally, there may be a second site spinal injury, which occurs in 15% of SCI patients.

In the trauma center, the priority remains the maintenance of tissue oxygenation and perfusion, with particular attention to maintaining an adequate mean arterial blood pressure. In this regard, the spinal injury patient presents particular challenges. Immobilization of the cervical spine during intubation is essential and is best accomplished with fiberoptic or awake nasotracheal maneuvers. Mechanical respiratory efforts may be minimal when the injury level is C5 or higher. In these patients, muscular expansion of the rib cage is absent and diaphragmatic breathing may be weakened. Thus, intubation with in-line stabilization using two physicians may be the only option to quickly establish airway control and ventilation. Caution should be exercised in suctioning the oropharynx, as this may stimulate autonomic reflex arcs, causing profound bradycardia and even cardiac arrest. The emergent cricothyroidotomy for airway access must also be considered.

Cervical and high thoracic injuries may result in spinal shock, which can severely complicate the management of a patient already in hypovolemic shock. The clinical picture is hypotension with an associated bradycardia and often hypothermia. Treatment is with mild fluid resuscitation and continuous intravenous inotropic infusions possessing alpha-adrenergic properties to increase the heart rate, cardiac output, and vasomotor tone. Dopamine, because of its mixed alpha-and beta-adrenergic effects, is a useful medication to treat spinal shock. Acutely symptomatic bradycardia should be treated with intravenous atropine. Monitoring with pulmonary atrial catheters (e.g., Swan-Ganz catheters) can help determine the adequacy of perfusion and cardiac output.

Associated extraspinal injuries are common and must also be ruled out. This would be assessed in the "D" and "E" sections of the assessment. Because spinal column injuries are typically the result of severe traumatic mechanisms, the incidence of associated cranial, thoracic, abdominal, and orthopedic injuries is high. Priority must be given to the most life-threatening injuries. If the patient is stable and cooperative, an exam to determine the level of injury (e.g., the ASIA scale) is performed.

The diagnosis of a spinal column injury is based on the clinical examination and radiologic investigations. In an awake, non-intoxicated patient, the absence of pain along the spinal axis is useful to rule out injury. In these patients, a low-velocity injury may require no x-rays, and a high-velocity injury requires only limited plain x-rays. It is essential that radiographic evidence of spinal column injury be correlated with the clinical examination, as 15% of patients have injuries at multiple spinal segments. X-ray, computed tomography, and magnetic resonance imaging investigations are needed in patients who are not able to fully cooperate with the neurologic examination.

Radiographs are useful not only for the detection of but also for the classification of injuries. The fracture types, as well as the degree of cord compression, are particularly important aspects of the injury that determine the management strategy. For the cervical spine, plain lateral x-rays must include the C7-T1 junction, as 31% of injuries occur between C6 and T1. In large, bulky patients, downward traction on the shoulders, a swimmer's view, or a computed tomography scan of the cervical spine may be needed to properly visualize the cervicothoracic junction. Lateral x-rays allow evaluation of vertebral alignment (> 3 mm subluxation suggests instability), canal diameter (normal is > 12 mm), angulation of the intervertebral space (normal is < 11°), width of the interspinous gap, and the atlantodental interval (the distance between the anterior margin of the dens and the closest point on the anterior arch of C1, which should be 3 mm in adults). Soft tissue swelling in the prevertebral space is an indirect indicator of cervical spine injury (maximum prevertebral space in adults at C1 is 10 mm, C2–4 is 5 to 7 mm, and C5–7 is 22 mm).

In the thoracic and lumbar spine, anterior compression fractures and fracture dislocations are usually clearly visible on lateral x-rays. Splaying of the interspinous ligaments is indicative of disruption of the posterior tension band, comprised of the spinous processes and the interspinous ligament. Burst fractures may be difficult to detect on a lateral x-ray but are evident from an abnormally increased intrapedicular space when compared to adjacent levels. Computed tomography is particularly useful in burst fractures for assessing the degree of canal compromise by retropulsed bone fragments from the vertebral body.

If the patient is otherwise systemically stable, cervical traction using a halo frame or Gardner-Wells tongs may be used to restore alignment of the cervical spine and to reduce neural compression. Traction must be initiated with caution, however, as neurologic deterioration can occur from overdistraction or movement of acutely herniated disk material [65]. Before traction is initiated, a full set of x-rays and a magnetic resonance imaging scan help to reduce the likelihood of worsening deficits. In the subaxial spine, it is prudent to begin with 10 lbs and to add weight until reduction is achieved or a total of 5 lbs per cervical level has been used. Serial lateral x-rays or fluoroscopic images should be taken and repeat physical exams performed after each addition of weight to ensure that the neck and spine have not been overdistracted. Of note, not all spine surgeons advocate the routine use of MRI in all cervical spine injuries [66]. Care should be also taken to avoid traction when possible in patients with ankylosing spondylitis because further fracture and·distraction of the vertebral column is likely.

Early intervention to prevent delayed sequelae should also be initiated at this point. This would include use of good respiratory therapy (e.g., incentive spirometry), GI prophylaxis (e.g., H-blockers), and pulmonary embolism prophylaxis (e.g., heparin derivatives, supportive stockings, and sequential compression devices).

ANATOMY

The human vertebral column consists of 7 cervical, 12 thoracic, 5 lumbar, and 1 fused sacrococcygeal vertebrae. A plum line

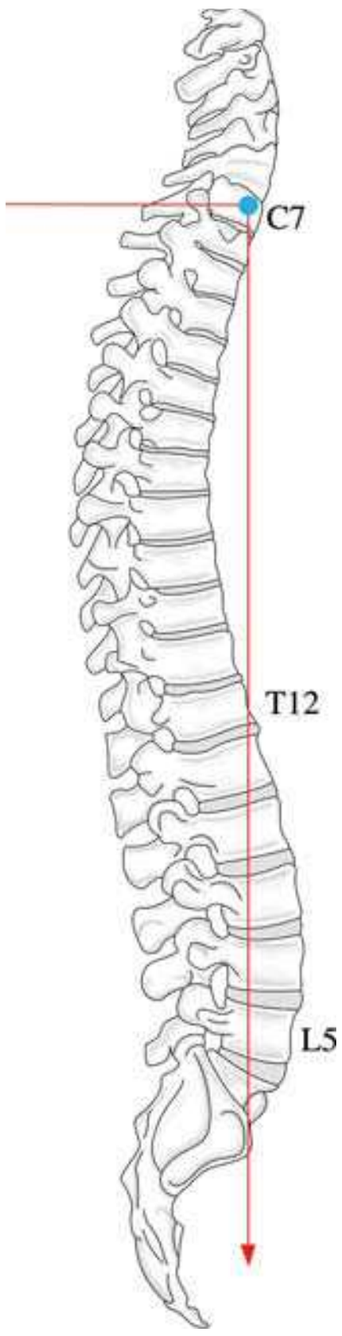

FIGURE 163.1. Sagittal balance image.

dropped from the C7 vertebra, tracing an imaginary line of gravity, runs anterior to the vertebral column in the thoracic and somewhat posterior in the lumbar regions. The line should normally fall near the sacral promontory. This is known as "sagittal balance" (Fig. 163.1).

The cervical canal is wider at the Cl and C2 levels, below which the canal diameter slowly tapers caudally. The lumbar canal is slightly wider than the thoracic canal. The greatest degree of flexion and extension occurs at the atlanto-occipital junction, and the greatest rotatory capability occurs at the atlantoaxial joint. Cervical vertebrae have transverse foramina that transmit the vertebral artery, which usually enters between C6 and C7.

The rib cage and costovertebral ligaments afford an additional element of stability compared with either the cervical or the thoracolumbar junction. Therefore, more force is required to produce a fracture in the mid thoracic spine region than the cervical or lumbar region. By the same token, less mobility is afforded in the thoracic spine [67]. The facet joint plane in the thoracic region is more sagittal than the cervical spine, but more coronal than the typical lumbar spine. The combination of these factors protects against rotational injury and allows somewhat more axial rotation.

The vascular supply of the spinal cord comprises the single anterior spinal artery, the paired posterior spinal arteries, and the segmental radicular arteries. The anterior spinal artery supplies the anterior two thirds of the cord, and the posterior spinal arteries supply the posterior third of the cord. In the cervical cord, the main vascular supplies come from the spinal arteries, but in the thoracic and lumbar regions, the segmental radicular arteries are the major contributors of blood supply. In the upper thoracic cord, the vascular supply may be sparse, especially between the fourth and eighth vertebrae, creating the watershed zone [68], which may be prone to hypotensive and hypoxic insults. The artery of Adamkiewicz (artery of lumbar enlargement) usually arises from T8 to T12 on the left side, most commonly arising from T10 to T12 on the left.

At the thoracolumbar junction and distally, the vertebral bodies allow a greater degree of motion. The lack of rib cage support, the increased room for flexion-extension, and the change in disc size and shape may all contribute to the relatively greater mobility of the lumbar spine. However, the additional degree of mobility at the thoracolumbar junction, especially from Tll to L2, makes this region more susceptible to injury than other adjacent portions of the spine. Because the middle and upper thoracic regions are relatively fixed, the thoracolumbar junction acts as a zone of mechanical stress concentration. The conus medullaris usually resides between the Tll and the Ll-2 disc space, and could be compromised by injuries at this level.

BIOMECHANICS OF INJURY AND STABILITY

Because the neural and musculoskeletal components of the human spine are intimately associated, any discussion regarding blunt traumatic spinal cord injury requires an understanding of the vertebral column. Concepts of stability in the vertebral column are complex. This reflects the intricate nature of the arrangements of joints in the spinal column. Each vertebra has multiple sites of articulation and interaction with the neighboring vertebra (intervertebral disks, facet joints, connecting ligaments). To maintain the stability of this naturally flexible structure, the body must incorporate a complex array of muscles and ligaments.

The vertebral column serves to transmit loads, to permit motion, and to protect the spinal cord. Instability of the spinal column may then be defined as its failure to perform any of these functions under physiologic levels of mechanical loading. This failure may occur acutely or in a progressive, delayed manner. In cases of traumatic spinal cord injury, the vertebral column acutely fails to shield the neural elements from external forces as a result of being stressed beyond its mechanical tolerances.

Various classification schemes have been devised to predict if the spine is unstable. The most common of these is the

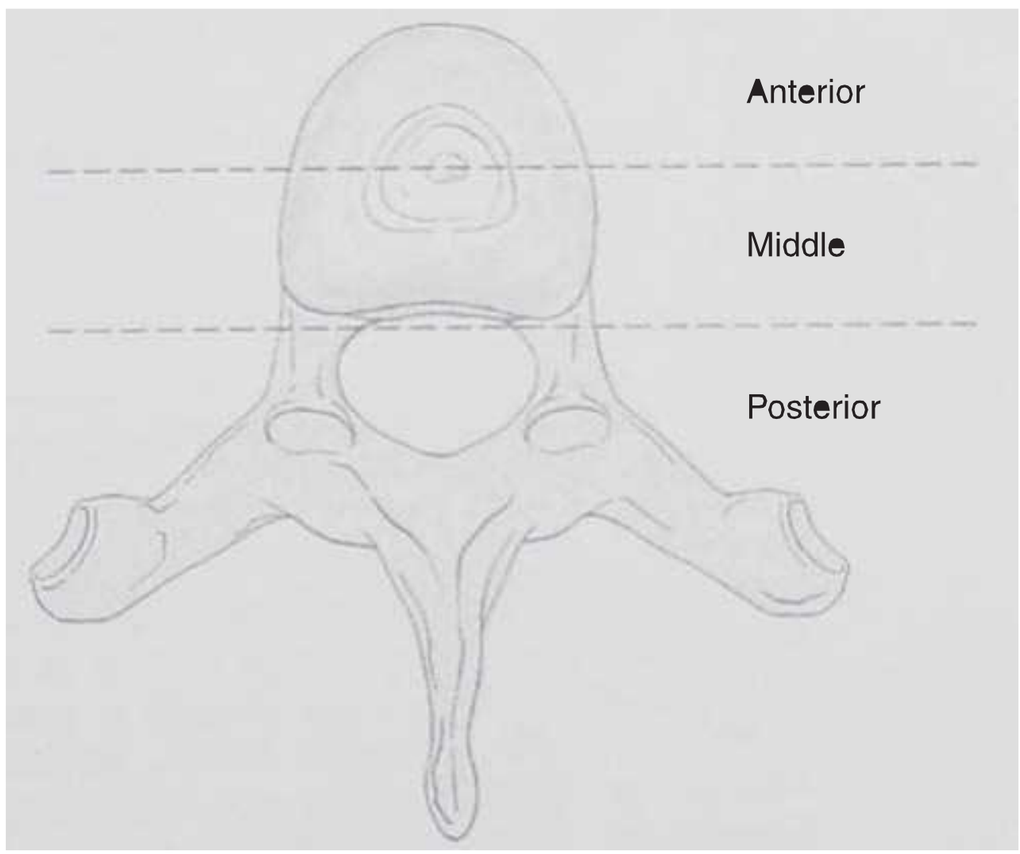

FIGURE 163.2. Denis three-column injury model.

three-column theory introduced by Denis [69,70] (Fig. 163.2). Although these concepts were originally based on studies of thoracolumbar fractures, these principles have been applied successfully to other regions of the spine. This classification system divides the spine into anterior, middle, and posterior columns. The anterior column consists of the anterior half of the vertebral body, the anterior half of the intervertebral disk, and the anterior longitudinal ligament. The middle column consists of the posterior half of the vertebral body, the posterior half of the intervertebral disk, and the posterior longitudinal ligament. The posterior column consists of the posterior arch, the facet joint complex, the interspinous ligament, the supraspinous ligament, and the ligamentum flavum. The diagnosis of instability is made if two or more of the columns are compromised.

External forces placed on the spine include axial compression, distraction, flexion, extension, and translation. Axial compression in the cervical spine results in disruptions of the ring of Cl and burst fractures of the remaining vertebrae. Axial compression in the thoracolumbar spine results in burst fractures. When compressive forces are applied anterior to the spinal column and result in a component of flexion, anterior compression fractures result. Severe flexion is the most common injury mechanism in the cervical spine. This can cause odontoid fractures, teardrop fractures of the vertebral bodies, dislocations of the vertebral bodies, and jumped facets. In the thoracolumbar spine, severe flexion results in compression of the anterior vertebral body. If the fulcrum of force is anterior to the vertebral column, as occurs when a seat-belted passenger is involved in a motor vehicle accident, a flexion-distraction injury of the thoracolumbar junction may result. If the injury passes through the disk space or through the vertebral body, a "chance fracture" may occur (Fig. 163.3).

White and Panjabi [67] recommended a systematic approach to stability, and devised a checklist to determine it. In an adult cervical spine, horizontal subluxation more than 3 mm or an angulation more than 11 degrees is considered unstable [71]. Fractures or alignment patterns that suggest substantial disruption of the bony/ligamentous structures on radiographs suggest injury. Other more complex systems to measure spine stability have also been developed [72].

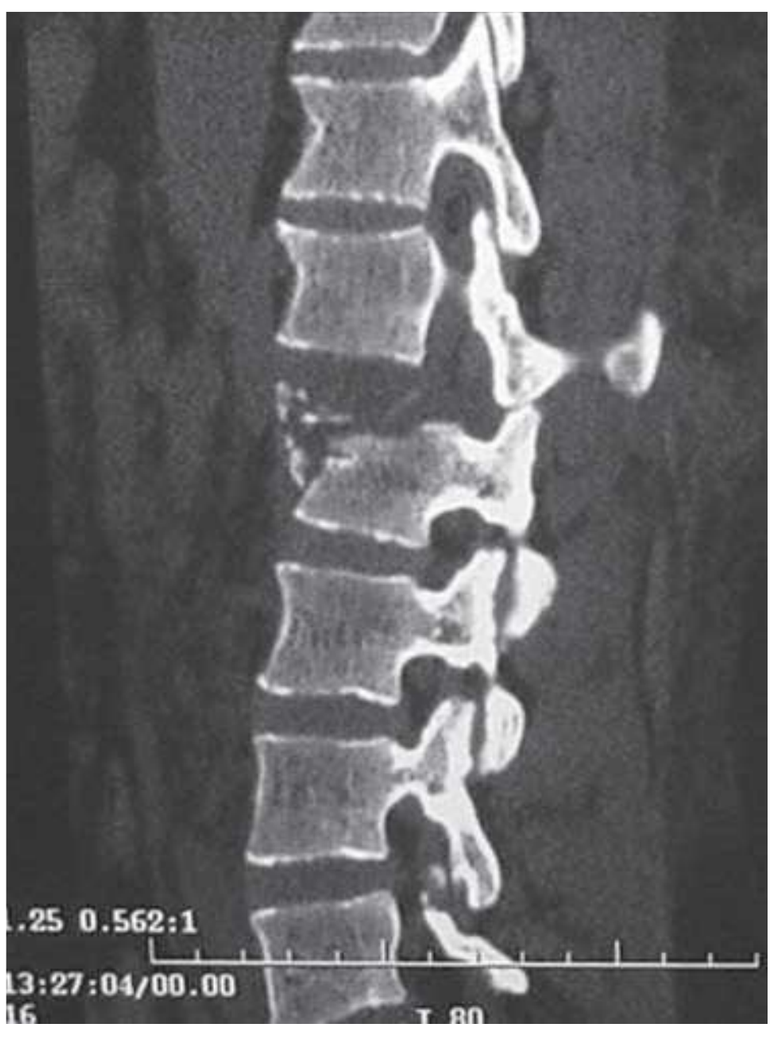

FIGURE 163.3. Radiographic image of chance fracture.

Instability of the spinal column requires maintenance of spinal precautions and bracing. In many instances, surgical realignment, fixation, and fusion will be necessary. Of note, missile injuries do not usually destabilize the spine.

TREATMENT

Initial (Field)

As the ABCDEs of trauma assessment are completed, the surgeon must reach certain goals. Maintaining an airway while stabilizing the spine is paramount. Blood pressure should be maintained to assure perfusion. Suggested levels are SBP >120 mm Hg and MAP >90 mm Hg. All unconscious patients (e.g., major blunt trauma victims) must be assumed to have an SCI until proven otherwise. A rigid backboard and cervical collar should be used to stabilize the spine.

Surgical

Radiologically proven compression of the spinal cord and nerve roots mandates surgical intervention for decompression and stabilization in the incomplete patient (e.g., ASIA B, C, or D).

Neural compression typically results from acute displacement of bone fragments, disruption of ligaments, and disk herniation. Delayed spinal cord compression may also develop from an expanding hematoma within the spinal canal or an inadequately immobilized spine where a prolapsed disk or bone could dynamically compress the cord. Late deterioration of motor or sensory function would prompt a clinician to search for a cause such as post-traumatic syringomyelia and/or progressive deformity. Overall, loss of neurologic function when compared to admission occurs in approximately 3% of patients [51].

Surgery for patients with complete loss of neurologic function remains controversial. Early surgical stabilization within the days after injury has more recently become popular because of the increasing safety of general anesthesia. Early stabilization allows for safe mobilization of the patient, physical and occupational therapy, and improved pulmonary toilet. Surgery for patients who have suffered severe injuries to vital organs may have to have their surgeries delayed. In these cases, maintenance of spinal precautions with a cervical collar and strict "log rolling" for nursing care should prevent deterioration.

The question of whether emergent surgery to the spinal cord improves the neurologic outcome remains controversial [11,33,34,65,73–76]. To directly answer this question, the STASCIS trial (Surgical Treatment of Acute Spinal Cord Injury Study) has been initiated. In this ongoing study, patients with cervical SCI, ASIA scores A, B, C, D, are identified and enrolled in this multicenter study. Patients were stratified into "early" (<24 hours) or "delayed" (>24 hours) groups based on time to decompression. (Decompression occurred by either cervical traction or surgery). At a 1-year follow up, 25% of patients in the early decompression group had a 2 or more grade improvement in ASIA score as compared to the delayed group, with 0% ($p = 0.009$). These results suggest that early decompression (within 24 hours of injury) is the most favorable course of action to treat traumatic SCI [77]. However, there are criticisms of the study. The study has a significant selection bias as the groups are noncontrolled. However, experimental models in animals do suggest that earlier decompression maximizes recovery [78].

Reviews of patients from the National Inpatient Sample allow comparisons between conservative treatment and laminectomy and/or fusion for patients with SCI. When compared to nonsurgical SCI patients, patients with surgery had

longer lengths of hospital stay (14 days vs. 9 days), but had lower mortality rates (3% vs. 7%) [10]. Other reviews of the literature provide somewhat contradictory conclusions regarding lengths of stay and neurological improvement [74].

PHARMACOLOGIC THERAPY FOR SPINAL CORD INJURY

Animal models of spinal cord injury have offered the hope that damage caused by secondary injury can be mitigated by early pharmacologic intervention. Three large, randomized, multicenter clinical trials have investigated the use of high dose methylprednisolone for spinal cord injury [13,79]. The standard dose is 30 mg per kg intravenous (IV) methylprednisolone over 1 hour, then 5.4 mg per kg per hour over the next 24 hours.

There has been a great deal of controversy surrounding the quality of the NASCIS trials, leading some authors to conclude that any possible benefits from high-dose methylprednisolone are outweighed by the increased incidence of steroid-related complications [15,16,80,81]. The authors of this chapter no longer use steroids for the treatment of acute spinal cord injury.

Trials of novel pharmacologic interventions for spinal cord injury are currently underway in both clinical and animal models. The therapies include using pharmaceuticals such as riluzole [1,30,82], minocycline [1,30,33,83], polyethylene glycol [1,30,84], erythropoietin [1,30], hypertonic saline [24,85–89], and Cethrin® [1,33]. Injections of autologous macrophages [90–93] and the application of hypothermia [18,19,20,22,23,94,95] are also being investigated. None of these therapies have been shown to be completely safe or effective for the treatment of acute spinal cord injury as of the date of this publication, although several are under clinical trial investigations.

MEDICAL MANAGEMENT OF SPINAL CORD-INJURED PATIENTS

The SCI patient presents unique challenges for the medical team providing both acute and chronic care. As with many other patients, those SCI patients with multiple comorbidities and advanced age are more likely to have poorer outcomes [10]. Several medical problems are frequently associated with a vertebral fracture or spinal cord injury. Some are related to the systemic effect of spinal cord injury, and the others are related to paralysis and prolonged immobilization. The concepts of kinetic therapy and the Roto-Rest treatment table (or similar devices) is endorsed by these authors as a means of minimizing the high morbidity associated with the effects of paralysis and immobility in all of the body systems following acute spinal cord injury.

Cardiovascular

Hypotension and bradycardia from spinal shock may be present. Management with titrated dopamine to support BP and atropine to increase heart rate are recommended. The patient may demonstrate autonomic hyperreflexia or dysreflexia, which is periodic autonomic instability triggered by stimuli such as bladder filling or catheterization when the injury occurs at or above the T6 level. The patients often describe exaggerated autonomic responses, including headache, flushing, diaphoresis, and paroxysmal hypertension. The effects of autonomic hyperreflexia may be life threatening if associated with hypertension. The treatment is to remove offending stimuli, such as by bladder decompression or bowel disimpaction. If a patient is in crisis, sublingual Procardia may be used to help avert a hemorrhagic stroke while one searches for the aggravating factors.

Pulmonary

The risk of pulmonary complications clearly increases with higher-level injuries due to the loss of phrenic nerve innervations (C3–5). For patients with injuries at C1–4, tracheostomy and prolonged mechanical ventilation are probably required. In patients with lower-level injuries, however, all attempts should be made to avoid a tracheostomy. For high cervical injury, one could consider a diaphragmatic pacemaker [96–98]. All injuries above T5 will have significant loss of inspiratory/expiratory force and volume given intercostals denervation.

Respiratory diseases account for 28% of deaths and are the leading cause of mortality in the first year after spinal cord injury [99]. Spinal injury patients are at high risk for pulmonary infection for a number of reasons. Prolonged poor pulmonary toilet, an inability to clear upper airway secretions, poor respiratory capacity, nosocomial exposure, weakened immune responses, and any accompanying chest trauma all increase the risk of pneumonia. The judicious use of aggressive suctioning, pulmonary toilet (e.g., incentive spirometry), chest physiotherapy, bronchodilators, positive-pressure ventilation, and bronchoscopic airway clearance helps prevent infection. Severe atelectasis can also cause respiratory distress in the absence of infection. The authors of this chapter advocate kinetic therapy (the Roto-Rest treatment table) to minimize the risks of pulmonary complications. The placement of an abdominal binder can minimize paradoxical respiratory effort and increase respiration.

Upper Gastrointestinal and Nutrition

All patients should have a nasogastric tube placed to suction drainage in the emergency room, as immobilization predisposes the patient to aspiration. Post-traumatic ileus is also common in this patient population. An indwelling gastric or duodenal tube also allows for early feeding as soon as any ileus has resolved. This supplementation is critical after trauma, as the energy demand of the patients is roughly 150% of their basal requirement. Special attention must also be directed at meeting the patient's increased protein requirements. Proper nutritional support prevents catabolism, supplements wound healing, and maximizes immune protection [27,100]. Parenteral appropriate until the ileus resolves, but tube feeding should begin as early as possible. Even small feeds through a nasogastric tube ("trophic feeding") may reduce the risk of sepsis through enterocyte nutrition.

Gastric ulcers are common in spinal cord injury patients, and this risk is increased with the use of high-dose methylprednisolone. Gastrointestinal hemorrhage is less common and occurs in 3% of patients [101]. H_2-blockers, proton-pump inhibitors, and sucralfate appear to be similarly effective in reducing the risk of gastrointestinal hemorrhage. GI protection is also especially important in patients receiving high-dose steroids. Pancreatitis and acalculous cholecystitis can also occur, especially if parenteral nutrition is used for prolonged periods of time. These disorders can be diagnosed by elevated amylase and bilirubin levels, respectively. Early recognition of these disorders depends on a high level of clinical vigilance. Since the SCI patient may have lost sensation of the abdomen, cardinal signs of acute abdomen e.g., rebound) may not be present.

Lower Gastrointestinal and Genitourinary

Immediately after a complete spinal cord injury the bladder is acontractile. Indwelling catheterization allows bladder drainage and measurements of fluid balance. Intermittent catheterization every 4 to 6 hours should commence as soon as possible to reduce the risk of urinary tract infections. These infections are common and should be treated aggressively to prevent urosepsis. The presence of urea-splitting organisms also increases the incidence of renal stone formation [101]. In addition, clinicians should be aware of autonomic dysreflexia, where an out of proportion sympathetic response may be elicited from a distended bladder or distended bowel. The person with SCI (often a T2 or higher injury) who presents to the emergency department with tachycardia, hypertension, severe headache, and so on, needs to be properly diagnosed rapidly. Often a simple treatment (bladder catheterization, bowel disimpaction) may be what is primarily required [102]. Other causes include decubitus ulcers, undiagnosed fistulae, or other infectious lesions. Sublingual Procardia may provide quick relief of hypertension. This relief can be life sparing.

After severe spinal injury, rectal tone is most often flaccid in lower motor neuron injuries. Constipation can easily occur unless manual evacuation is carried out on a regular basis. The liberal use of rectal suppositories stimulates bowel emptying, and regular doses of stool softener should also be used. New surgical procedures to restore manual bladder control are available [40,103]. Devices to aid in defecation are also being investigated and developed [38].

Clinicians should be aware of the systemic effects that SCI has on the reproductive system, especially in men [104–106] and should be prepared to counsel the patient on his options.

Infectious Disease/Fever

The "5 W's" of fever workup are relevant for the SCI patient: Wind (atelectasis), Water (urinary infection), Wound (wound infection), Walk (DVTs), and Weird (drug reactions.) Routine lab analysis should be part of the initial workup for fever. These include erythrocyte sedimentation rate (ESR) and C-reactive protein as infection markers. One should also order tests such as urine analysis and culture for UTI, duplex ultrasound for DVTs, blood cultures for sepsis, skin inspection for breakdown or infection, liver function tests (LFTs) including total and direct bilirubin, amylase, and lipase for hepatitis, acalculous cholecystitis, or pancreatitis. Again, it is important to note that SCI patients may be unable to alert physicians to common signs (e.g., leg pain, abdominal pain) due to their injuries.

Cutaneous and Musculoskeletal

Pressure ulcers are common after spinal cord injury and occur in up to 25% to 30% of patients (101). Transport on hard backboards, prolonged immobilization, loss of cutaneous sensation, and reduced skin perfusion all predispose to skin breakdown. The sacrum, heels, ischium, and occiput are most commonly involved.

Prevention of pressure ulcers begins in the emergency room. Patients should be removed from the backboard and any hard surfaces as soon as possible, as pressure necrosis of the skin can occur in less than 1 hour on these surfaces. In the acute care setting, the patient should be turned in a "log roll" fashion every 2 hours until the spine is proven to be stable or until the spine is stabilized surgically. Alternatively, an electrically driven kinetic bed such as the Roto-Rest (Kinetic Concepts, San Antonio, TX) or other pressure relieving beds or mattress overlays can be used [107].

Stage I lesions can be managed with aggressive mobilization and adhesive barrier dressings. Once the dermis has been compromised, however, daily sterile dressing may be needed for wound debridement. Deeper lesions may require debridement and skin grafting in the operating room. Proper management of even mild lesions prevents devastating late sequelae such as sepsis from infected ulcers. The development of the "VAC" aided healing of severe decubitus ulcers provides gentle suction which debrides and reduces the size of the ulcer. Relief of the pressure source and debridement and cleaning of the wound is essential. The patient must be given a high protein diet to facilitate decubitus ulcer healing. In the subacute and chronic setting, muscle denervation leads to atrophy, spasticity, and contracture formation. Passive range of motion exercises and splinting forestall the formation of contractures. Etidronate sodium and increasing mobility may reduce heterotopic ossifications [108]. Proper nutritional support is essential.

Thromboembolism

The combination of trauma, paralysis, and immobility places paralyzed patients at high risk of developing deep venous thrombosis and pulmonary embolism. The incidence of lower-extremity venous thrombosis varies widely in literature reports depending on the test used (fibrinogen scanning, clinical, impedance plethysmography, venography). Rates ranging from 12% to 81% have been reported. The highest reported frequency of PE was approximately 5% [109]. PE is responsible for 10% of all deaths after SCI [99]. The risk of PE peaks at 2 to 3 weeks after injury.

These authors advocate the use of the Roto-Rest kinetic treatment table (or similar devices) for all acute spinal cord injury to combat pulmonary emboli. Routine use of pneumatic compression devices and subcutaneous heparin (or similar drugs) can reduce the risk of thromboembolism [110–112]. For example, 5,000 units of subcutaneous heparin can be administered twice daily within the first 2 days of injury. The prophylactic use of a vena cava filter is advocated by some, but controversy exists [113,114]. For patients who are not able to utilize to pneumatic compression devices and prophylactic heparin, vena cava (temporary or permanent) filters are a recommended option [115–118].

Psychosocial

All acute spinal cord injury patients experience psychological sequelae to their catastrophic injury. Most often, family and friends experience similar effects including denial, depression, anger, and finally coping. The coping phase is when the person decides to deal with the realities of their disability, although not to accept that their paralysis is "forever." A team of caring physicians and other health professionals including rehabilitation psychologists is essential for a number of psychosocial actions. Antidepressants can also be helpful in certain cases.

The spinal cord injured community has unique needs. This community is not a homogenous group, as different levels of injury will leave the person with SCI with different amounts of residual function. As such, the immediate needs of the person with SCI are also not uniform. When asked what problems if addressed would lead to the greatest increase in quality of life, the people with high cervical injuries (quadriplegics) identified restoration of hand and arm use as the most important. People with lower injuries (paraplegics) identified bladder, bowel, autonomic dystrophy, and sexual function as the most important issues to address [35]. Listening to the needs of this

community will help researchers develop practical improvements to help the SCI community.

SPINAL CORD INJURY IN CHILDREN

By adolescence the spine is well developed and the patterns of injury resemble those of adults. Perhaps because of the increased mobility of the developing spine, pediatric spinal cord injuries are rare [119]. Because of the greater proportional mass of the head, however, children are more susceptible to atlanto-occipital injuries. The hypermobility of the pediatric spine also accounts for cases of spinal cord injury without radiographic abnormality (SCIWORA). This represents 15% to 20% of all pediatric spinal cord injuries [120,121].

The principles in managing pediatric spinal cord injuries are similar to that of adults. Because children cannot cooperate fully with the physical examination, it is important to recognize subtle physical and radiologic signs. As such, an increased reliance must often be placed on radiographic studies. Many of the standard measurements used to evaluate cervical x-rays need to be adjusted for the pediatric spine.

In young children, the increased relative size of the head compared to body results in neck flexion when placed on a rigid backboard. This malalignment can accentuate deformity in cervical spine and should be avoided. Equipment tailored

TABLE 163.2

COMPLETED PROSPECTIVE RANDOMIZED CONTROLLED SCI CLINICAL TRIALS[a]

Trial name	Year	No. of patients	Study design	SCI type, treatment window (h)	Treatment arms	Conclusions
NASCIS I	1984	330	Phase III RCT	I, 48	MPSS 100 mg × 10 d MPSS 1000 mg × 10 d	No difference
NASCIS II	1990	487	Phase III RCT	C/I, 12	MPSS (24 h) Naloxone Placebo	Negative primary analysis; secondary analysis showed improved recovery if treated w/MPSS win 8 h of injury; naloxone negative
Maryland GM-1	1991	34	Phase II RCT—pilot study	I, 72	GM-1 Placebo	Improved neurological recovery w/GM-1 in this small pilot study
Otani et al.	1994	158	Nonblinded RCT	?, 8	MPSS (NASCIS II 24 h) Placebo	Significantly more steroid-treated patients had some sensory improvement, no motor differences
TRH	1995	20	Phase II RCT—pilot study	C/I, 2	TRH Placebo	Suggestion of improved neurological recovery w/TRH in this small pilot study
NASCIS III	1997	499	Phase III RCT	I, 12	MPSS (24 h) MPSS (48 h) MPSS bolus then TM	Improved neurological recovery w/ MPSS if administered early (w/in 3 h after SCI); TM not superior to MPSS
Nimodipine	1998	100	Phase III RCT	C/I, 6	Pimodipine MPSS (24 h) Nimodipine + MPSS (24 h) Placebo	No difference; study likely underpowered to detect a difference
Gacyclidine	1999	280	Phase II RCT	C/I, 2	Gacyclidine (0.005 mg/kg) Gacyclidine (0.01 mg/kg) Gacyclidine (0.02 mg/kg) Placebo	Negative study; trend to improved motor recovry w/imcomplete cervical injuries
Pointillart et al.	2000	106	Blinded RCT	?, 8	MPSS (NASCIS II 24 h) Nimodipine MPSS & nimodipine Placebo	No neurological differences between groups; trend to increased infections in groups receiving MPSS
Sygen (GM-1)	2001	797	Phase III RCT	I, 72	MPSS & low-dose GM-1 MPSS & high-dose GM-1 MPSS & placebo	Negative primary outcomes; trend to improved secondary outcomes

[a]Further trials are not planned for any of the agents presented in this table, to the knowledge of the authors.
C, complete; I, incomplete; RCT, randomized controlled clinical trial; TM, tirilizad mesylate; ?, unpublished or unclear data.

for pediatric spine immobilization should be used whenever possible. Unlike adults, the majority of these injuries can be treated nonsurgically with bracing [122].

FUTURE ADVANCES

Approximately 100 years ago at the beginning of the 20th century, Dr. Alfred Reginald Allen induced a spinal cord injury in an animal model for the purpose of understanding SCI [123]. His advancements were not alone, as the 20th century was remarkable for incredible advances in science, medicine, engineering, and technology. Many of these advances have helped to make the opening years of the 21st century, 2001 to 2010, the "decade of the spine."

In the realm of Basic Science research, there have been great advances in understanding the pathophysiology of SCI [1,5,6,82]. Understanding of the mechanisms of inflammation, cell migration, immunology, and cell death allow for basic scientists to identify pathways that can be directly targeted in future clinical investigations. Understanding biochemical environment of the region of the SCI allows scientists to better engineer biological repair strategies. For example, understanding the inhibitory properties of the glial scar after an injury may allow scientists to target and overcome these obstacles [9].

The surgical realm continues to advance, with improvements in spine fusion techniques and hardware. Clinical studies, like STASCIS [33,77,76] also allow the clinician to best judge the optimal time to initiate treatment. New and innovative devices are coming to market to stabilize and repair the bony, ligamentous, and disk injuries that often accompany SCI [124–131].

Additional studies into autologous (e.g., macrophage, oligodendrocyte, Schwann) and stem cell transplantation, tissue engineering, and hypothermia are being actively pursued to further develop methods to preserve function or to restore function to the person living with an SCI [1,9,19,33,41,45,93,132–138]. Hypothermia research suggests that cooling patients with SCI may protect neural tissue from secondary injury by increasing tissue tolerance to reduced blood flow and oxygenation. Efficacy and safety studies of moderate hypothermia (32°C to 34°C) are currently under investigation [19].

New medical therapies are being tested. Minocycline is being tested in a Canadian trial [83,139,140] as a treatment to reduce oligodendrocyte and microglial apoptosis. Riluzole, a sodium channel inhibitor, is also in multicenter trials [1,104,139]. Rho inhibitors are also being investigated. This includes Nogo, a critical inhibitor of neural regeneration by inhibition of guanosine triphosphatase (GTPase). Local injection of anti-Rho antibodies is in a phase II study [141].

Oscillating field stimulation to promote axonal regrowth along the cranial/caudal plane (as opposed to random orientation) is being studied as well [142,143].

There have been studies to bypass the injured CNS and to tap directly into the brain, allowing a person with SCI to control simple machines [144–150]. These are adaptive strategies such as Functional Electrical Stimulation (FES), Robotics and Brain Machine Interfaces.

The hope of neural restoration remains the focus of intense basic science research. Whether through stem cell transplantation, molecular manipulation, or modulation of the local cytokine milieu, the aim is to restore function to cells that have already been damaged or destroyed. Because reinnervation of the spinal cord is the best way to fully restore neurologic function, research in this area remains the primary goal at the Miami Project to Cure Paralysis.

Despite all of the exciting advances forthcoming in the field of spinal cord injury, prevention of injury remains a top priority. Programs such as the Think First initiative in Florida have already dramatically reduced the incidence of diving-related cervical spine injuries. Physicians, who are most acutely aware of the devastating consequence of spinal cord injury, must assume a key role in educating the public on how to avoid these catastrophic injuries.

SUMMARY OF RECOMMENDATIONS BASED UPON RANDOMIZED CONTROLLED CLINICAL TRIALS

A recent review of completed clinical trials has been published by Dr. Fehling's group. Completed trials are reproduced as Table 163.2, and ongoing clinical trials are reproduced as Table 163.3 [139].

Unfortunately, there is no consensus on the single best treatment available for a spinal cord injury. At present, there are multiple options available for treatments that include hypothermia, reduction by traction, and surgical decompression. Fortunately, there are ongoing clinical trials to aid clinicians in future decision making and with evidence-based medicine. One such example comes from our department at the University of Miami. Allan Levi and colleagues have been investigating hypothermia in treating Spinal Cord Injury in clinical settings [94,95].

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CHAPTER 164 ■ THORACIC AND CARDIAC TRAUMA

SCOTT B. JOHNSON AND JOHN G. MYERS

INTRODUCTION

Thoracic trauma is responsible for 20% to 25% of the estimated 150,000 trauma related deaths per year in the United States and is the leading cause of death in the first four decades of life. Two thirds of thoracic-related deaths occur in the prehospital setting, usually due to significant cardiac, great vessel, or tracheobronchial injuries. In a study of over 1,300 patients presenting to a level I trauma center with thoracic trauma, Kulshrestha and colleagues reported an overall mortality rate of 9.4%, with 56% of these occurring within the initial 24 hours. While the two strongest determinants of increased mortality were a low GCS and increased age, penetrating injury, liver or spleen injury, long bone fracture, and more than five rib fractures also adversely affected mortality [1]. In a study of trauma-related hospital deaths at an urban level I trauma center, Demetriades and colleagues found a penetrating mechanism, age more than 60, and chest AIS > 3 to be significant variables associated with patients who had no vital signs on admission [2].

Overall, motor vehicle collisions account for 70% to 80% of all thoracic injuries. The incidence of penetrating injuries varies widely but is usually more prevalent in urban centers. The majority of thoracic injuries can be treated with careful observation or tube thoracostomy. It is historically reported that 12% to 15% of patients with thoracic injury will require thoracotomy. In a Western Trauma Association multicenter review, only 1% of all trauma patients required nonresuscitative thoracotomy [3]. With the improvements in prehospital care and transport, more of the severely injured patients who would have previously died at the scene are making it to the hospital alive. Success in the management of these injuries rests in having a high index of suspicion for the life-threatening thoracic injuries, prompt recognition and treatment of associated injuries, and aggressive management of coexisting pulmonary dysfunction.

INDICATIONS FOR URGENT SURGICAL INTERVENTION

Bleeding

Hemothorax is second only to rib fractures as the most common associated finding in thoracic trauma, being present in approximately 25% of patients with thoracic trauma. Bleeding can arise from the chest wall, lung parenchyma, major thoracic vessels, heart, or diaphragm. A small or moderate-size hemothorax that stops bleeding immediately after placement of a tube thoracostomy can usually be managed conservatively. However, if the patient continues to bleed at a rate of more than 200 cc per hour, exploration is indicated. The accumulation of more than 1,500 cc of blood within a pleural space is considered a massive hemothorax and is an indication for exploration. If the patient becomes hemodynamically unstable at anytime and an intrathoracic source is suspected, emergent thoracotomy should be performed irrespective of chest tube drainage. A chest radiograph should always be obtained after placing a tube thoracostomy to ensure proper position of the tube and complete drainage of the pleural space. Video-assisted thoracoscopic surgery (VATS) can be considered in the stable patient with retained hemothorax or in a stable patient who continues to bleed at a slow but steady rate; however, the surgeon should not hesitate to convert to open thoracotomy if visualization is inadequate or drainage and evacuation of the pleural space is incomplete.

Cardiovascular Collapse

The indications for resuscitative emergency department thoracotomy (EDT) continue to be debated. Our indications, which are considered to be fairly liberal, include (1) loss of vitals

in the Emergency Department for both blunt and penetrating trauma and (2) loss of vitals en route, with less than 10 minutes of prehospital CPR, with some sign of life upon arrival, or a suspected intrathoracic etiology. Penetrating thoracic injuries, specifically stab wounds, have the highest rate of survival. Data for blunt trauma are much less encouraging but should not be used as a deterrent, as there are several functional survivors in most reported series. A retrospective study of 959 patients undergoing resuscitative thoracotomy concluded that EDT in blunt trauma with more than 5 minutes or penetrating trauma with more than 15 minutes of prehospital CPR is futile care [4]. When performed, resuscitative thoracotomy should be performed early. Discovered tamponade should be released; massive pulmonary bleeding should be quickly controlled with staplers, clamping, or manual compression; and cardiac wounds should be controlled. With no intrathoracic source, the aorta should be clamped and internal cardiac massage continued.

Massive Air Leak

Findings on initial presentation of significant subcutaneous emphysema, a subsequent large or persistent air leak, or persistent pneumothorax should alert the clinician to the presence of a major tracheobronchial injury. This injury is potentially lethal but relatively rare, found in only 2% to 5% of patients with thoracic trauma. Significant tracheobronchial injuries may result in a massive air leak, leading to hypoventilation. Maneuvers to stabilize the patient should include decreasing airway pressures. Contralateral mainstem intubation can also be attempted. Major tracheobronchial injuries generally should be repaired as early as the patient's condition allows.

Tamponade

Cardiac tamponade results when fluid or air collects within an intact pericardial sac, resulting in compression of the right heart with subsequent obstruction of venous return and cardiovascular collapse. Potential findings upon presentation include tachycardia and hypotension, cervical cyanosis, jugular venous distension, muffled heart sounds, and pulsus paradoxus. The diagnosis is confirmed with echocardiography, pericardial window, or at the time of emergent thoracotomy. Treatment requires prompt resuscitation and decompression of the pericardium, followed by repair of the bleeding source.

DIAGNOSTICS

Diagnostic imaging plays a key role in the management of patients after chest trauma and has considerable impact on therapeutic decision-making. The information generated by diagnostic imaging procedures not only serves to tailor therapy to the individual needs of the patient, but also helps to determine overall prognosis and outcome. Radiologic imaging plays an important role in the workup of any patient with suspected chest trauma. The chest radiograph is the initial imaging study of choice to be obtained in patients with suspected chest injury. Chest Computed Tomography (CT), however, is being used with increasing frequency in the evaluation of patients with chest trauma. CT can be useful in assessing suspected traumatic aortic, pulmonary, airway, skeletal, and diaphragmatic injuries. Magnetic resonance imaging (MRI) on the other hand has a limited role in the initial evaluation of any patient with suspected chest trauma. To undergo an MRI, the patient must be stable, and many trauma patients cannot be scanned because of bulky, mechanical supportive equipment. However, in selected patients who are hemodynamically stable, MRI may be particularly useful for the evaluation of spine and diaphragm injuries. Other imaging modalities available to the clinician include echocardiography, angiography, and VATS, which can be both diagnostic and therapeutic when appropriately indicated.

Plain Chest Radiograph

The frontal chest radiograph is the most appropriate initial radiographic study to obtain for the evaluation of patients with suspected chest injury. This study is particularly useful in helping to rule out major injury. Ideally, the radiograph should be obtained with the patient in the upright position because of mediastinal widening that is typically seen in the supine position. Chest radiography has a 98% negative predictive value and is therefore quite useful when normal. However, abnormal findings may be subtle and quite nonspecific. Radiographic findings that may indicate mediastinal injury, such as major aortic disruption, include abnormal contour or indistinctness of the aortic knob, apical pleural cap, rightward deviation of the nasogastric tube, thickening of the right paratracheal stripe, downward displacement of the left mainstem bronchus, rightward deviation of the trachea, and, not uncommonly, nonspecific mediastinal widening. Most life-threatening injuries can be screened by the plain chest radiograph and a careful physical exam. Blunt thoracic injuries detected by CT alone infrequently require immediate therapy. If immediate therapy is needed, findings will usually be visible on plain radiographs or obvious on clinical exam. Although a plain upright chest radiograph remains one of the basic imaging studies routinely performed on initial screening, it may be over-utilized. A recent study suggests that in the presence of a normal physical exam in the hemodynamically stable patient, obtaining a routine chest radiograph is actually unnecessary, since it rarely, if ever, changes clinical care [5].

Chest Computed Tomography

CT is highly sensitive in detecting thoracic injuries after blunt chest trauma and is superior to routine CXR in visualizing lung contusions, pneumothorax, and hemothorax, and it can often alter initial therapeutic management in a significant number of patients with suspected chest trauma. It has also been shown to detect unexpected injuries and abnormalities, resulting in altered management in a substantial number of patients when applied appropriately [6]. It can be particularly useful in screening for major intrathoracic aortic injury. In one study, contrast-enhanced CT scanning was 100% sensitive in detecting major thoracic aortic injury based on clinical follow-up and was 99.7% specific, with 89% positive and 100% negative predictive values for an overall diagnostic accuracy of 99.7% [7]. An unequivocally normal mediastinum at CT, with no hematoma and a regular aorta surrounded by a normal fat pad, has essentially a 100% negative predictive value for aortic injury [7–10]. It has also been shown that CT scanning detects 11% of thoracic aortic injuries that are not detected by routine, plain chest radiography alone [11].

CT scanning can also be useful in detecting hemopericardium and/or hemothorax from any cause, injury to the brachiocephalic vessels, pneumothorax, rib fractures, pulmonary parenchymal contusion, and sternal fractures. It can also be useful in detecting pneumomediastinum caused by pulmonary interstitial emphysema, bronchial or tracheal rupture (commonly associated with pneumothorax), esophageal rupture, or iatrogenic injury from over-ventilation or traumatic intubation. In addition, CT scanning can detect injuries otherwise missed by routine plain radiograph. In one study comparing CT

scanning with plain radiography, CT scanning detected serious injuries in 65% of those patients not found to have injury on plain film. These injuries included (in decreasing order of frequency) lung contusions, pneumothoraces, hemothoraces, diaphragmatic ruptures, and myocardial ruptures [12]. Even in those patients without suspected chest trauma, CT scanning of the abdomen, which commonly includes the lower portion of the thorax, often yields important information regarding possible intrathoracic injury. In one study, hematoma surrounding the intrathoracic aorta near the level of the diaphragmatic crura seen on intra-abdominal CT scanning was found to be a relatively insensitive but highly specific sign for thoracic aortic injury after blunt trauma. Therefore, the presence of this sign seen on abdominal CT imaging should prompt more specific imaging of the thoracic aorta to evaluate potential thoracic aortic injury [13]. CT scanning has also been shown to be useful to help define the extent of pulmonary contusion and identify those patients at high risk for acute pulmonary failure in those patients with PaO_2/FIO_2 lower than 300. 3-D CT scanning has also been shown to be useful in diagnosing and determining the severity of sternal fractures [14]. With the advent of high resolution CT scanners that can reconstruct axial, coronal, and sagittal images, even penetrating diaphragmatic injuries, which are difficult to image preoperatively, can be diagnosed with a relatively high sensitivity and specificity [15]. Despite its usefulness however, thoracic CT scanning is not necessarily routinely indicated for all patients with chest wall trauma. In addition, although there has been a dramatic increase in the utilization of CT scanning in the last decade, its usefulness in detecting clinically relevant injury has recently come into question, especially in those patients with a normal screening plain chest radiograph [16].

Ultrasound

Transesophageal echocardiography (TEE) is rapidly gaining acceptance as an important diagnostic tool available to the trauma surgeon and is showing particular promise in diagnosing traumatic intrathoracic aortic injuries. Although somewhat invasive, its portability makes it a diagnostic procedure of choice in looking at the heart and great vessels in multiply injured trauma patients. In one particular study of 58 patients with thoracic trauma, TEE demonstrated its usefulness in diagnosing thoracic aortic injury and permitted the identification of small lesions not detectable by CT scanning or angiography [17]. TEE has shown to be an important diagnostic tool for examining the thoracic aorta and is valuable in identifying aortic injury in high-risk trauma patients who are too unstable to undergo transport to the aortography suite. Nienaber et al. prospectively compared TEE with aortogram in evaluation of nontraumatic aortic dissection and found the technique to be a safe and highly sensitive method of diagnosing lesions of the descending aorta, with accuracy approaching 100% [18]. When an aortic injury is present, typical findings on the TEE can include aortic wall hematomas, intimal flaps, or disruptions. Several groups have shown TEE to be accurate in identifying aortic pathology after trauma, with its diagnostic efficacy mainly limited by the experience of the person performing the exam [19–21]. In addition, it has been shown to be useful in diagnosing blunt cardiac rupture, when other diagnostic modalities have failed, as well as in diagnosing severe valvular regurgitation intraoperatively following foreign body removal [22,23].

Numerous studies report that transthoracic echocardiography (TTE) is emerging as an effective noninvasive screening examination for pericardial effusion in the trauma setting. Although subxiphoid pericardial window is currently considered the gold standard to confirm the diagnosis of pericardial tamponade, conventional 2-dimensional TTE has been shown to reveal as little as 50 mL of blood within the pericardium and can show cardiac pseudoaneurysms and the location of foreign bodies [24–27]. Lopez et al. [28] showed that TTE can detect and distinguish hemopericardium from other effusions of lower echogenicity. In prospective studies of patients sustaining penetrating precordial injuries, TTE demonstrated sensitivities of 56% to 90%, with specificities of 93% to 97%. Its overall accuracy was 90% to 96% [29,30]. Because TTE is an examination that can be performed at the bedside, it can be performed rapidly and may decrease the time to diagnosis versus pericardial window (15.5 minutes vs. 42.4 minutes in one study by Meyer et. al.) [30]. It has also been shown that earlier therapeutic intervention facilitated by TTE may be associated with improved survival [31]. In addition, TTE has been shown to be able to identify cardiac sources for hemodynamic instability in the operating room unrelated to tamponade, such as the relatively rare case of atrioventricular valve rupture, which would otherwise be difficult to diagnose, therefore allowing for expeditious repair using cardiopulmonary support [32]. Thus, both TTE and TEE are emerging as useful screening modalities that can be used to evaluate both penetrating and blunt cardiac injuries.

Angiography

Thoracic aortography historically has been the gold standard for diagnosing thoracic aortic injury and for defining the extent of the injury and involvement of branch disease, if present. Aortography usually requires approximately 40 mL of a nonionic iodinated contrast material injected at a rate of 18 to 20 mL per sec. At least two views are obtained—one in the anteroposterior plane and another usually at a 45 degree left anterior oblique projection. If these do not accurately visualize the areas of concern, then additional views may be necessary, either from a lateral or a right anterior oblique projection. Diagnosis of aortic injury angiographically is usually made by finding one or more of the following: an irregular or discontinued contour of the aortic lumen, an intimal flap, an aortic dissection, and/or a luminal outpouching (i.e., pseudoaneurysm). Thoracic aortography can detect blunt traumatic aortic injuries with 96% sensitivity and 98% specificity. False negative examinations are usually related to incomplete or inadequate injections or projections. To be an adequate study, the aortic root as well as the distal descending thoracic aorta should be visualized since these locations are involved, respectively, with 8% and 2% of all blunt thoracic aortic injuries. False positives usually relate to a prominent ductus diverticulum or from an ulcerated atheromatous plaque. A ductus diverticulum can be seen in up to 9% of thoracic aortograms and is related to a remnant of the enlarged mouth of the ductus arteriosus. It appears as a localized bulge of the anterior wall of the aorta and can be differentiated from a pseudoaneurysm due to its usually smooth, regular, symmetrical borders; intimal disruption is typically absent. In addition, the aortic lumen adjacent to the diverticulum is not narrowed, and there is absence of retention of contrast upon the washout phase of the angiogram, which is often typical of pseudoaneurysms. Ulcerated atheromas usually are small, isolated outpouchings of the aortic wall with a collar button appearance. They are typically located in the mid-descending aorta rather that at the aortic isthmus. It is not uncommon for them to occur in individuals that demonstrate widespread atherosclerotic disease and should, therefore, be suspected on angiograms obtained in clinically relevant individuals. Angiography is invasive and can have associated complications. The complications associated with arteriography include allergic reactions, renal failure, local puncture site problems, stroke, and even death. Radiographic contrast media cause severe anaphylactic reactions in less than 2% of cases. A prior history of allergic reaction to intravascular contrast material increases the risk for a subsequent reaction, even after premedication with histamine

blockers and steroids. Patients with preexisting comorbidities, such as renal disease, diabetes mellitus, congestive heart failure, or who are elderly (over 70 years of age) have the highest risk for acute renal dysfunction following contrast administration. The reported incidence of contrast-induced nephropathy varies from less than 1% in the general patient population to as high as 92% among patients with comorbidities that predispose to renal insults, such as diabetes and renal insufficiency [33].

Arteriography requires arterial puncture with cannulation, usually percutaneously. Possible entry sites include not only the femoral artery (most common) but also the axillary and brachial arteries. Possible puncture site complications include hematoma, pseudoaneurysm, arteriovenous fistula, hemorrhage, arterial thrombosis, and femoral neuralgia. Fortunately, clinically significant local arterial complications occur in only 0.1% to 5% of cases. The risk of complications is also related to the indication for arteriography. Fortunately, the lowest risk for complications occur in trauma patients and the complication rates quoted in older studies may not accurately reflect current risk.

Video-Assisted Thoracoscopic Surgery

The role of thoracoscopy in trauma has been explored by a number of investigators in the literature. Prior to the modern video era, Jones et al. described management of 36 patients with thoracoscopy under local anesthesia as a diagnostic tool to define intrathoracic injuries and to visualize ongoing hemorrhage [34] Four patients in their series were spared abdominal exploration when the diaphragm was found devoid of injury. More recently, Ochsner et al. [35] and Mealy et al. [36] have demonstrated the usefulness of VATS as a diagnostic tool in the assessment of diaphragmatic integrity in cases of penetrating and blunt thoracic injuries respectively. VATS has become an acceptable surgical modality in the diagnostic evaluation of suspected diaphragmatic injury and has been shown to have therapeutic benefit when evacuation of clotted hemothoraces is able to be performed in stable patients with penetrating chest injures [37]. Main indications for VATS include diagnosis and treatment of diaphragmatic injuries, diagnosis of persistent hemorrhage, management of retained thoracic collections, assessment of cardiac and mediastinal structures, diagnosis of bronchopleural fistulas, and diagnosis and treatment of persistent posttraumatic pneumothorax. VATS has been shown to be a useful alternative to an open thoracotomy in selected patients. Because lung deflation with single-lung ventilation is a critical component of the technique, VATS is relatively contraindicated in patients unable to tolerate this. Caution should be used in patients with suspected obliteration to their pleural cavity secondary to previous infection ("pleurisy") or surgery. VATS should have no role in the management of unstable patients or in those patients unable to tolerate formal thoracotomy for any reason. Whether VATS should be considered as the initial approach in evaluation of all stable chest trauma patients when an intrathoracic injury is suspected is still debated, and appropriate patient selection remains important.

SPECIFIC INJURIES

Chest Wall

Rib Fractures

Rib fractures are a common injury and are often associated with other injuries. Rib fractures themselves usually cause only minor problems; however, they may be a marker of more severe injury, and it may be the underlying pulmonary contusion that often accompanies the rib fracture that may be more clinically relevant. A study by Flagel et al. showed that 13% of those patients in the National Trauma Data Bank who had one or more rib fractures (n = 64,750) developed complications including pneumonia, acute respiratory distress syndrome, pulmonary embolus, pneumothorax, aspiration pneumonia, empyema, and the need for mechanical ventilation. They also showed that increasing number of rib fractures correlated directly with increasing pulmonary morbidity and mortality. The overall mortality rate for patients with rib fractures was 10%. The mortality rate increased ($p < 0.02$) with each additional rib fracture, independent of patient age. This ranged from 5.8% for a single rib fracture to 10% in the case of 5 fractured ribs. The mortality rate increased dramatically for the groups with 6, 7, and 8 or more fractured ribs to 11.4%, 15.0%, and 34.4%, respectively [38]. Interestingly, in their study epidural analgesia was associated with a reduction in mortality for all patients sustaining rib fractures, particularly those with more than four fractures. Since this was not a prospective randomized study, it is difficult to tell if there was a correlation between patients that received epidural catheters having an overall lower injury severity score. However, in one prospective randomized trial by Bulger et al., trauma patients with rib fractures were randomized to either receive epidural anesthesia or intravenous opioids for pain relief, and it was shown that those patients with epidural anesthesia had a lower incidence of nosocomial pneumonia and shorter duration of mechanical ventilation [39]. The number of patients that could receive epidural anesthesia was limited, however, due to strict inclusion criteria. The age of the patient sustaining rib fractures should be taken into account, as well as the location of the fractures. It has been shown that rib fractures occurring in the very young should alert the clinician to possible nonaccidental trauma (NAT). In one study by Barsness et al., rib fractures in children under 3 years of age had a positive predictive value of NAT of 95%, and rib fracture was the only skeletal manifestation of NAT in 29% of the children [40]. With regards to the elderly, it has been shown that there is a linear relationship between age and complications, including mortality. It has been shown that elderly patients with rib fractures have up to twice the mortality of younger patients with similar injuries [41]. In addition, this increase in mortality may begin to be seen in patients as early as 45 years of age when more than four ribs are involved [42]. The location of the rib fracture(s) is also important, as it has been shown that left-sided rib fractures are associated with splenic injuries, and right-sided rib fractures are associated with liver injuries. While isolated rib fractures have an associated incidence of vascular injury of only 3%, first rib fractures in association with multiple rib fractures have a 24% incidence of associated vascular injury. A first rib fracture along with findings of a widened mediastinum, upper extremity pulse deficit, brachial plexus injury, and/or expanding hematoma should prompt work-up for a possible subclavian arterial injury.

Flail Chest

Flail chest occurs when multiple adjacent ribs are broken in two locations, thereby allowing that portion of the chest wall to move independently with respiration. The strict definition of flail chest is the fracture of at least four consecutive ribs in two or more places; however, the functional definition is an incompetent segment of chest wall large enough to impair the patient's respiration. Major mortality and morbidity of flail chest can be attributed to the usual underlying associated pulmonary contusion and the hypoventilation/hypoxia that results from the paradoxical movement of the chest wall. This is a mechanical problem in which negative pressure generated during inspiration within the thorax is dissipated by movement of the flail segment inward. This movement equalizes the intrathoracic

pressure, which would normally be accomplished by the movement of air into the lungs. In addition, the underlying pulmonary contusion usually leads to a ventilation perfusion mismatch, contributing to the hypoxia; the pain associated with multiple rib fractures can lead to splinting and contribute to hypoventilation. As a result, both oxygenation as well as ventilation is compromised. Usually a large number of ribs have to be involved to be clinically significant. Fortunately, this occurs relatively rarely with rib fractures. Flagel et al. showed an overall incidence of flail chest of 3.95% in patients with 6 rib fractures; 4.84% in those with 7 rib fractures; and 6.42% in those with 8 or more rib fractures [38].

The basic treatment for flail chest injury has not changed appreciably over the last several decades. Ventilatory support in the form of mechanical, positive pressure ventilation remains the gold standard against which all other forms of treatment are measured. Avery et al. coined this type of treatment "internal pneumatic stabilization" in 1956 [43]. Positive pressure ventilation, which effectively forces the flail segment to rise and fall normally with inspirations, effectively allows stabilization of the flail segment with respect to the remainder of the chest wall. Surgical stabilization of the chest wall has been shown to be of some benefit with regard to shorter length of ventilator dependency, lower rates of pneumonia, and shorter intensive care unit stays, although this form of therapy is not yet widely practiced [44]. Pain control continues to be an important adjunct in any treatment regimen.

Sternal Fracture

Sternal fractures have been shown to decrease the stability of the thorax in cadavers [45]. They usually occur as a deceleration force during traffic accidents together with blunt force trauma from foreign objects, such as steering wheels, although they have been reported as a complication of CPR, which interestingly was found in 14% of medical autopsy cases that had received chest compressions prior to death [46]. Traffic accidents are the cause of sternal fractures in almost 90% of cases, with approximately 25% of fractures graded as moderately to severely displaced. Approximately 30% of patients will have associated injuries, with craniocerebral trauma and rib fractures being the most commonly associated injuries [47]. Displaced fractures are more likely to have associated thoracic and cardiac injuries and are more likely to require surgical fixation.

However, the majority of patients can be safely observed and even discharged home as long as the following criteria are met: (1) the injury is not one of high-velocity impact, (2) the fracture is not severely displaced, (3) there are no clinically significant associated injuries, and (4) complex analgesic requirements are not required. Most serious complications and deaths that occur in patients with sternal fractures are not due to the fracture itself but rather are related to the associated injuries, such as flail chest, head injury, or pulmonary or cardiac contusion. Although approximately 22% of patients will exhibit electrocardiographic changes, elevated creatine kinase MB isoenzymes, or echocardiographic abnormalities, only approximately 6% of patients will exhibit a clinically significant myocardial contusion. In addition to myocardial contusion, other complications of sternal fracture such as mediastinal abscess, mediastinitis, and acute tamponade have all been reported. Indications for operative sternal fixation are certainly not absolute and should be judged individually. Generally accepted criteria include severe pain, sternal instability causing respiratory compromise, and severe displacement. Only a small percentage of patients (2% in one series) actually require sternal fixation [48]. A lack of consensus among surgeons on how to treat these injuries, in addition to a lack of randomized trials concerning their optimal approach, continues to prevail.

Scapular Fracture

Scapular fractures are relatively rare and were once presumed to be an indicator of severe underlying trauma and subsequent higher mortality. They occur in only approximately 1% to 4% of blunt trauma patients who present to a level I trauma center and are associated with a higher incidence of thoracic injury compared to those patients who sustain blunt trauma without a scapular fracture. However, more recent studies have indicated that although patients with scapular fractures tend to have more severe chest injuries and a higher overall injury severity score, their length of intensive care unit stay, length of hospital stay, and overall mortality is not necessarily increased [49,50]. Treatment is usually conservative and, most of the time, necessarily aimed at the associated injuries that are commonly present.

Scapulothoracic Dissociation

Scapulothoracic dissociation is an infrequent injury with a potentially devastating outcome. Scapulothoracic dissociation results from massive traction injury to the anterolateral shoulder girdle with disruption of the scapulothoracic articulation. Identification of this injury requires a degree of clinical suspicion, based upon the injury mechanism and physical findings. Assessment of the degree of trauma to the musculoskeletal, neurologic, and vascular structures should be made. Based upon clinical findings, a rational diagnostic approach can be navigated and appropriate surgical intervention planned. Scapulothoracic dissociation frequently is associated with acromioclavicular separation, a displaced clavicular fracture, subclavian or axillary vascular disruption, and a sternoclavicular disruption. Clinically, patients usually present with a laterally displaced scapula, a flail extremity, an absent brachial pulse, and massive swelling of the shoulder. Vascular injury occurs in 88% of patients and severe neurologic injuries occur in 94% of patients. Many of these patients have a poor outcome and present with a flail, flaccid extremity that usually results in early amputation and have an overall mortality of 10%. One of the most devastating aspects of scapulothoracic dissociation is the brachial plexus injuries that occur, which are typically proximal, involving the roots and cords—brachial plexus avulsions are not unusual. Attempts at repair of complete brachial plexus injuries with grafts or nerve transfers have generally been unsuccessful [51]. Treatment includes arterial and venous ligation to stop exsanguination if present, orthopedic stabilization and consideration for above elbow amputation electively, if brachial plexus avulsion is present, to allow for a more useful extremity. Overall prognosis for limb recovery is poor.

Traumatic Asphyxia

Traumatic asphyxia occurs as a result of a sudden or severe compression injury of the thorax or upper abdomen. It is most often associated with blunt trauma secondary to a crush injury. Entrapment of children under automatic garage doors is a prime example, as reported by Kriel et al. [52]. The true incidence of traumatic asphyxia is unknown, but it is considered to be a relatively rare event. The diagnosis is usually made based on the mechanism of injury and physical examination. Associated injuries are common and therefore should be investigated. The usual physical findings consist of facial edema, cyanosis, and petechial hemorrhages of the upper torso, neck, and face. The petechiae usually occur within the conjunctiva and oral mucosa and become most prominent a few hours after the initial injury. Neurologic findings are not rare and are thought to be secondary to anoxic injury, as well as possible cerebral edema and hemorrhage. The exact pathophysiology is thought to be due to a crushing injury applied to the mediastinum, which causes the heart to force blood out of the right

atrium retrograde into the valveless innominate and jugular venous system. In addition, a sudden reflexive inspiration is thought to occur against a closed glottis, which may elevate the intrathoracic pressures to high levels. This results in a sudden and rapid increase in the pressure of the small veins of the face and neck, resulting in the typical petechial hemorrhages that are observed.

Treatment is generally supportive. Specific therapy for traumatic asphyxia is based on physiologic techniques to decrease intracranial pressure, including elevation of the head of the bed and oxygen therapy. The need to treat possible associated injuries may take priority. Commonly associated injuries include rib fractures, pulmonary contusions, extremity fractures, pneumothorax, hemothorax, flail chest, and blunt pelvic and intra-abdominal injuries (i.e., splenic and/or liver lacerations). The prognosis of patients with traumatic asphyxia is generally good, as long as the patient did not sustain prolonged apnea or hypoxia. The majority of fatalities are usually from associated injuries and their complications. When death does occur, it usually occurs in patients who have sustained a prolonged compression, causing massive irreversible neurologic insult from the resultant apnea and hypoxia.

Pleural Space

Pneumothorax

This section will only focus on pneumothoraces associated with trauma. For further general discussion of pneumothorax in the critically ill, readers are referred to Chapter 57. For in depth discussion of imaging studies on the topic of pneumothorax, readers are referred to Chapters 57 and 63. A traumatic pneumothorax occurs from either blunt or penetrating trauma, with resultant direct injury to the pleural barrier. Rib fractures may or may not be present. Mechanical ventilation can also be considered a traumatic cause of pneumothorax and has an overall associated incidence of 5%. This incidence increases dramatically in patients with underlying lung diseases, such as COPD and acute respiratory distress syndrome (ARDS). Iatrogenic causes of pneumothorax are also prevalent within the hospital setting. Central-line insertions are associated with a 3% to 6% incidence of pneumothorax.

All types of pneumothorax may progress to tension pneumothorax, which occurs in 1% to 3% of spontaneous pneumothoraces and can occur at any stage of treatment. As tension pneumothorax is a rapidly progressive condition, early identification is essential and immediate decompression should be performed when suspected on clinical grounds.

Tension pneumothorax is a clinical diagnosis, and treatment should never be delayed to obtain a confirmatory radiograph. Open pneumothorax is caused when a penetrating chest injury opens the pleural space to the atmosphere. Open pneumothorax may also occur with massive blunt trauma that literally rips open the chest. This leads to a collapsed lung and a "sucking" chest wound. Open pneumothorax is an injury commonly seen on the battlefield. In civilian life, impalement by objects is a common cause. In injuries where the chest wall wound diameter approaches two thirds of the diameter of the trachea, air will preferentially enter the pleural space through the wound during respiration, thereby inhibiting normal ventilation through the upper airway, leading to profound hypoventilation and subsequent hypoxia. Changes in venous return can occur similar to that seen in a tension pneumothorax, which in turn can lead to hemodynamic instability. The presence of a "sucking" chest wound makes the diagnosis obvious. External wound size may not correlate with the degree of compromise, as it is the size of the atmospheric-pleural connection that is most correlative.

Treatment includes appropriate resuscitative maneuvers, including securing the airway, adequate ventilation, and locating the wound and placing a sterile occlusive dressing over it to allow negative pressure ventilation to resume. If this does not suffice, intubation and positive pressure mechanical ventilation may be necessary. A standard method of coverage involves placing a nonporous dressing over the wound and taping it on three sides, allowing it to act as a one-way valve, allowing air to escape during expiration but occlusive during negative pressure inspiration. A chest tube is routinely sterilely inserted at a separate site away from the site of injury to treat any possible tension pneumothorax that may arise. The wound should be cared for locally and associated injuries should be sought and treated appropriately.

Hemothorax

After rib fractures, hemothorax is the second most common complication of chest trauma. It can be caused by bleeding from anywhere in the chest cavity, including the chest wall, lung parenchyma, major thoracic vessels, heart, or diaphragm. It presents in approximately 25% of patients with chest trauma. Patients with hemothorax typically have decreased breath sounds and dullness to percussion over the affected side with associated dyspnea and tachypnea. Depending on the amount of blood loss, they may be in hemodynamic shock. The major cause of significant hemothorax is usually due to a laceration to the lung or bleeding from an injured intercostal vessel or internal mammary artery. Radiographic films may not reveal a fluid collection of less than 300 mL. Small hemothoraces usually seal themselves within a few days. Accumulation of more than 1,500 mL of blood within a pleural space is considered massive, is more commonly seen on the left side, and is usually due to aortic rupture (blunt trauma) or pulmonary hilar or major vessel injury (penetrating trauma). Massive hemothorax can lead to hemodynamic instability including hypotension and circulatory collapse. Neck veins may be flat or distended, depending on whether or not blood loss or increased intrathoracic pressure predominates. A mediastinal shift with tracheal deviation is typically away from the side of blood accumulation.

Treatment of acute hemothorax includes supplemental oxygen therapy and, in most cases, the insertion of a large bore (i.e., 36 French) tube thoracostomy anterior to the midaxillary line at the fifth or sixth intercostal space. A moderate-size hemothorax (500 to 1,500 mL) that stops bleeding immediately after a tube thoracostomy can usually be managed conservatively with a closed drainage system. Bleeding from pulmonary parenchymal injuries that do not involve the hilum usually will stop on their own because of the low pulmonary pressures and high concentrations of tissue thromboplastin within the lung [53]. If, however, the patient continues to bleed at a rate of 100 to 200 mL per hour, then exploration is indicated. Likewise, if the patient bleeds out more than 1,500 mL initially through the chest tube, exploration is indicated. If the patient is hemodynamically unstable at any time, and intrathoracic bleeding is suspected as the cause, emergent thoracotomy should be done regardless of chest tube output. A chest radiograph should always be obtained after placing a tube thoracostomy to check position of the tube and to make sure that the pleural space is adequately drained. If a large amount of retained blood and clot remains within the pleural space despite tube thoracostomy, exploration with open evacuation should be considered. VATS is an option in the stable patient with retained hemothorax or in a stable patient that continues to bleed at a slow but steady rate; however, the surgeon should not hesitate to convert to open thoracotomy if visualization is inadequate or drainage and evacuation of the pleural space is incomplete. If the retained hemothorax is not massive, nonoperative therapy

can be considered as these may lyse with time. Alternatively, it has been shown that a retained hemothorax can be successfully treated with instillation of thrombolytics into the pleural space. This has been deemed safe even in patients who have sustained multiple trauma [54].

Lung

Contusion

Pulmonary contusion is a common injury found in patients sustaining blunt chest trauma, with an approximate incidence of 30% to 75%. Mortality is between 10% and 25%. Hemorrhage and interstitial edema result from injury to the lung. This can lead to alveolar collapse and the typical parenchymal consolidation seen on radiograph. Injury to the parenchyma from blunt force trauma is thought to be caused by a combination of events that include alveolar stretching, parenchymal tearing, and concussive forces. Lung injury in the absence of identifiable rib fractures typically exhibits diffuse injury; whereas rib fractures and flail chest are associated with more localized injury. The extravasation of blood into the alveolar space causes subsequent consolidation which can then lead to an intrapulmonary shunt. A flail chest may be associated with pulmonary contusion in approximately three fourths of the time, which more than doubles the morbidity and mortality. Hypoxemia, although nonspecific, is the most common clinical finding associated with pulmonary contusion and should raise the suspicion of its diagnosis. Typical chest radiographic findings in the appropriate clinical setting remain the mainstay of diagnosis. Typical findings usually demonstrate a focal or diffuse consolidative process that does not typically follow anatomical segments or lobes. Rib fractures are the most common bony injuries seen and should raise suspicion for the diagnosis of pulmonary contusion, even if other clinical signs are absent at the time. Pulmonary contusion may not become radiographically apparent for up to 48 hours postinjury, with an average delay of 6 hours. On the other hand, CT scanning of the chest has been shown to be able to demonstrate the presence of pulmonary contusion almost immediately postinjury [55–58]. In addition, it can help estimate the total volume of injured lung present. This can be helpful in predicting the need for eventual ventilatory support. It has been shown that when pulmonary contusion involves 28% or more of the total lung volume, essentially all patients eventually require mechanical ventilation; whereas when 18% or less of the lung volume is involved, the need for mechanical ventilatory support is unlikely [59]. Treatment of pulmonary contusion is generally supportive. Close respiratory monitoring and frequent clinical examination is important, as approximately half of all respiratory failures secondary to pulmonary contusion occur usually within the first few hours postinjury. Once diagnosed and coexistent injuries are treated, and the need for emergent surgery is ruled out or performed as required, the patient should be transferred to a monitored bed. Good pulmonary toilet should be employed and may be achieved through several mechanisms, including nasotracheal suction, chest physiotherapy, and postural drainage. This helps to minimize atelectasis and expel bronchial secretions. If patients are still unable to clear their secretions adequately, bronchoscopy can be helpful. Adequate analgesia is also important in maintaining good pulmonary toilet. This can be achieved through nerve blocks, systemic opioids, or epidural anesthesia. Mechanical ventilation can minimize edema and increase functional residual capacity, which in turn can decrease shunting and reduce hypoxemia. Positioning patients with the injured lung in the nondependent position may also improve oxygenation, especially in those patients refractory to other measures. Fluid administration should be done judiciously, as hypervolemia may worsen fluid extravasation into the alveolar spaces and worsen parenchymal consolidation, especially since capillary permeability is already compromised. However, under-resuscitation should also be avoided, as this may lead to thickened secretions, possibly worsening cardiac output and shunt fraction. Obviously, fluid administration in these patients can be a difficult balancing act, and good clinical judgment is important. Positive end expiratory pressure (PEEP) should be maintained at the minimum value necessary to ensure adequate oxygenation, since excessive PEEP may actually worsen gas exchange and can actually extend the area of injury. Atelectasis can lead to infectious pneumonia, which typically begins to contribute more to the hypoxia after the initial couple of days postinjury. Pulmonary infections may develop in up to 50% of patients with pulmonary contusion. Furosemide, in addition to its diuretic affect, can be useful in the treatment of patients with pulmonary contusion. Acute respiratory distress syndrome (ARDS) can complicate pulmonary contusion in 5% to 20% of cases, and respiratory dysfunction is a common sequela that can be found in a majority of patients in the long term. Dyspnea may affect as many as 90% of patients during the first 6 months postinjury. In addition, functional reserve capacity has been found to be diminished as late as 4 years after injury, with the majority of patients demonstrating subtle changes on CT [60].

Tracheobronchial Injury/Lung Laceration

Tracheobronchial injury can be a challenge to diagnose, manage, and definitively treat. The true incidence of tracheobronchial injury is difficult to establish, as a large proportion (30% to 80%) of these patients will die before reaching the hospital. It is estimated on the basis of autopsy reports that 2.5% to 3.2% of patients who die as a result of trauma may have associated tracheobronchial injury [61,62]. More than 80% of tracheobronchial injury due to blunt trauma is located within 2.5 cm of the carina. Resuscitation of a patient with tracheobronchial injury can be difficult, since obtaining adequate ventilation may require novel approaches to secure the airway. Patients with tracheal or bronchial injuries make this initial assessment particularly challenging. The majority of patients with tracheobronchial injury seen in the emergency department have some degree of respiratory difficulty, and these patients may require emergent measures to secure and control the airway. Orotracheal intubation is the most common method used. Patients with cervical injuries and open neck wounds can be intubated through the open wound to secure the airway if necessary. The initial physical findings in patients with tracheobronchial injury can be subtle. However, several abnormalities can alert the physician to the diagnosis. Tachypnea and subcutaneous emphysema are common. Pneumothorax may or may not be seen on a plain radiograph. The liberal use of bronchoscopy is mandatory in identifying tracheobronchial injuries and constitutes the gold standard in diagnosis. Findings that can typically be seen on bronchoscopy include obstruction of the airway with blood and inability to visualize the more distal lobar bronchi because of collapsed proximal bronchi. Visualization of a bronchial tear is confirmatory. Associated injuries are common and are usually related to the mechanism and location of the tracheobronchial injury. The most commonly associated injury related to penetrating tracheobronchial injury is esophageal perforation. Most repairs of cervical tracheal injuries are approached through a collar incision. In patients with injuries high in the mediastinal trachea or with suspected great-vessel injury, a median sternotomy may be necessary. When the injury is associated with a unilateral pneumothorax or a bronchial injury is diagnosed preoperatively, an ipsilateral posterolateral thoracotomy is the incision of choice. For injuries to the mediastinal trachea, an approach by a right posterolateral

thoracotomy (usually high through the fourth intercostal space) is reasonable. Since the initial report by Shaw and colleagues, primary repair of the injured tracheobronchial tree has been encouraged [61,63–67]. Most patients can undergo primary repair of their tracheobronchial injury using tailored surgical techniques specific to the injury. When a major bronchus is disrupted, lobectomy is the preferred method of treatment, with closure of the bronchial stump debrided back to healthy tissue. With injuries to the mainstem bronchi, primary repair is preferred over pneumonectomy whenever possible, due to the higher mortality associated with pneumonectomy, especially in the trauma setting. Injury to the trachea can be either primarily repaired or converted to a tracheostomy if necessary for airway control. Nonoperative management of tracheobronchial injury has been reported to be successful in selected cases. Those patients that seem most appropriate for this approach are those with membranous injuries. Patients that have cartilaginous injuries are more likely to require operative repair. Tracheobronchial injury encompasses a heterogeneous group of injuries that requires skillful airway management, careful diagnostic evaluation, and operative repairs that are often creative and necessarily unique to the given injury.

Heart

Cardiac Contusion/Blunt Cardiac Rupture

Most blunt cardiac injuries are not serious. However, moderately severe cardiac injuries may cause arrhythmias or result in low-output cardiac failure. The clinical significance of myocardial contusion following blunt thoracic trauma is still largely unknown. In one study by Lindstaedt et al., approximately 20% of patients who were admitted to a surgical intensive care unit because of their injuries met the criteria for diagnosis of myocardial contusion [68]. Their criteria include exclusion of pathologic findings on ECG known to be present prior to injury; echocardiographic evidence of akinetic wall motion abnormalities; combination of regional wall motion abnormality, significant isoenzyme elevation (CK-MB > 7%), and ECG abnormality; regional wall motion abnormality in the baseline echocardiogram and in the control echocardiogram at follow-up; or confirmation of myocardial contusion at autopsy or intraoperatively. Even though the prevalence of the injury was significant in their population, the overall prognosis was excellent, and the authors recommend that specific diagnostic and therapeutic measures should be limited to cases where cardiac complications develop. The combination of a normal ECG and normal serum troponin levels, drawn at the time of presentation and 8 hours later, essentially rule out significant myocardial contusion and is sufficient, in the absence of other reasons for hospitalization, to discharge such patients safely home. However, patients with an abnormal ECG and elevated troponin should be monitored for at least 24 hours. Cardiac contusion may lead to cardiogenic shock resistant to inotropic support. The use of intra-aortic balloon counterpulsation as a mechanical means of augmenting cardiac function following cardiac contusion has been reported with success even in elderly patients [69]. Severe injuries to the heart can result in cardiac rupture. Atrial and/or ventricular rupture can occur, leading to profound hemodynamic compromise. Rapid recognition of such injuries is necessary for successful treatment. Associated injuries are common and include closed head injury, pulmonary contusion and/or laceration, multiple rib fractures, liver and spleen injury, and traumatic aortic injury; these account for approximately 25% of fatalities seen in patients with blunt cardiac injury. The usual clinical presentation of cardiac rupture is cardiac tamponade secondary to hemopericardium, although less than 15% of these patients actually manifest physiological evidence of tamponade. Associated pericardial tears may allow for decompression of intrapericardial hemorrhage through the pleural space, preventing the development of cardiac tamponade but leading to hemothorax. Pericardial rupture is rare, but can occur in isolation or with associated injuries such as blunt cardiac or diaphragmatic rupture, which has a high mortality. Hypotension is usually present, and the diagnosis of cardiac rupture should be considered in any patient who has hypotension in the absence of overt blood loss. The chest radiograph may not show evidence of cardiac injury, even in the face of tamponade and hemodynamic compromise, since a rapid accumulation of blood into the pericardial space can occur without significantly altering the cardiac silhouette. Echocardiography can be useful in diagnosing pericardial tamponade. Diagnosis of blunt cardiac rupture should be strongly suspected when hemopericardium is seen by ultrasound in the setting of blunt trauma. The diagnostic dependability of pericardiocentesis is limited in the assessment of traumatic hemopericardium and potential cardiac rupture because of significant false negative and false positive results. Performing a pericardial window in the operating room, however, can be both diagnostic and therapeutic, and it can confirm hemopericardium and allow for rapid decompression and median sternotomy. Nevertheless, the diagnosis of blunt cardiac rupture requires a fair degree of clinical suspicion, particularly in the setting of hypotension that does not respond to adequate volume resuscitation. Perchinsky et al. reviewed a consecutive series of 27 patients seen between 1984 and 1993 with blunt cardiac rupture. Overall survival rate was 41%. Of note was that three out of nine (33%) patients presenting to the emergency department with no identifiable blood pressure or viable electrical heart rhythm survived resuscitation, surgery, and initial hospital care. No patient survived rupture of two or more cardiac chambers in their series, however [70]. Although cardiac exploration should be performed with cardiopulmonary bypass support nearby, repair of cardiac rupture does not necessarily require its use.

Cardiac Valvular Injuries

Blunt cardiac injury may result in valvular insufficiency. The right ventricle is immediately behind the sternum, which makes it particularly vulnerable to injury. Acute severe elevation of right intraventricular pressures has been shown to result in injury of the tricuspid valvular apparatus [71]. The most common injury is chordal rupture, followed by rupture of the anterior papillary muscle and leaflet tears. Posttraumatic aortic valve regurgitation has also been reported and affects all ages and is often found in association with sternal or multiple rib fractures [72]. Traumatic mitral valve insufficiency has been shown to present with either complete papillary muscle avulsion from its ventricular attachment or with chordal tears and/or leaflet damage. Those with papillary muscle avulsion typically present with severe regurgitation. Those patients with less severe injuries to the mitral valve, such as chordal tears and/or leaflet damage, usually present with less severe symptoms and may even be asymptomatic. Not only can blunt cardiac injury cause acute valvular incompetence, but it can also predispose patients to delayed valvular dysfunction. In a study performed by Ismailov et al. looking at hospital patient discharges, patients who sustained blunt cardiac injury had an associated 12-fold increased risk for developing tricuspid valve insufficiency and a 3.4-fold increased risk of developing aortic valvular insufficiency later in life, which appeared to be independent of age, race, sex, and injury severity score [73]. There was no correlation found with increased risk for mitral valve insufficiency, however. Traumatic valve insufficiency, depending on severity and valve involved, may necessitate surgical treatment.

Penetrating Cardiac Injury

The clinical presentation of penetrating cardiac injury ranges from one of hemodynamic stability to complete cardiopulmonary arrest. Beck's Triad represents the classical presentation of the patient arriving in the emergency department in pericardial tamponade and includes venous hypertension, arterial hypotension, and muffled heart sounds. Kussmaul's sign, jugular venous distention seen with expiration, is another classic sign attributed to pericardial tamponade. The physiology of pericardial tamponade is related to the relative inelastic and noncompliant pericardium. Sudden acute loss of intracardiac blood volume into the pericardial sac leads to an acute pressure rise and compression of the thin-walled right ventricle and atria. This decreases the heart's ability to fill, resulting in decreased left ventricular filling and ejection fraction, thus decreasing cardiac output. Subxiphoid pericardial window remains the gold standard for the diagnosis of cardiac injury. It can also be therapeutic and can be done under local anesthesia in the operating room to allow release of tamponade prior to the induction of general anesthesia. If blood is found, then the surgeon can proceed immediately to median sternotomy and cardiorrhaphy. In relatively stable patients who do not require emergency room thoracotomy, median sternotomy is the incision of choice to repair penetrating cardiac wounds [74,75]. TTE has clearly emerged as the technique of choice for the diagnosis of penetrating cardiac injuries. Jimenez et al. showed that TTE had 90% accuracy, 97% specificity, and 90% sensitivity in detecting penetrating cardiac injuries [29]. The usefulness of echocardiography may be in its ability to identify obvious hemopericardium, thereby allowing the trauma surgeon to proceed directly to median sternotomy and thus eliminating the need for a subxiphoid pericardial window in many cases. Indications to perform EDT include loss of vital signs with suspected pericardial tamponade, especially in the case of suspected penetrating trauma to the heart. An anterolateral thoracotomy is typically performed in between chest compressions and should be extended through all of the subcutaneous tissues, as well as the anterior chest wall muscles, until the intercostal space is identified. Typically, the patient's vital signs quickly return to acceptable levels. Internal defibrillation may be necessary, as the heart is often found to be in ventricular fibrillation. Epinephrine and similar drugs should specifically be avoided, as release of the tamponade is usually more than sufficient to allow the patient's vital signs to return. Epinephrine can increase chronotropy, inotropy, and intraventricular pressures, which can potentially extend ventricular injuries and make repair difficult and unnecessarily challenging. If sinus rhythm cannot be restored despite all attempts, the prognosis is grave and the outcome is invariably poor. Once vital signs are reestablished, attention can then be given to repairing the cardiac injury. Definitive cardiac repair does not necessarily have to be done immediately, however, and in some cases may be ill-advised when performing an emergency room thoracotomy, since it is the tamponade and not the blood loss per se that causes hemodynamic collapse. Once the tamponade is released, digital pressure can be directly applied to the cardiac wound which is often all that is needed once vital signs are restored to maintain relative hemostasis until definitive repair can be done in an operating room. In the authors' opinion, the use of adjunct measures, such as balloon tamponade with a Foley catheter, can be fraught with creating more injuries or extending existing myocardial lacerations and should be avoided if possible. Vascular clamps can be placed on bleeding right atrial wounds but usually are not necessary and may cause more harm than not, extending small injuries into larger ones. In addition, cross-clamping of the thoracic aorta is generally not necessary and ill-advised with isolated penetrating cardiac wounds. If necessary, it can be temporarily occluded digitally against the bodies of the thoracic vertebrae until adequate resuscitation has taken place. An attempt should be made to trace the trajectory of the wounding agent, as missiles often enter into one thorax and then enter the contralateral hemithorax. Once the tamponade has been released, and the patient has regained a rhythm and a blood pressure and the bleeding sites are identified and digitally controlled, the experienced surgeon can then attempt closure of the cardiac wound in an appropriate equipped operating room. Total inflow occlusion of the heart can be done if the blood loss is substantial through the wound and proper placement of sutures difficult in the face of on-going blood loss without the aid of cardiopulmonary bypass. This maneuver is performed by placing caval tapes around both the superior and inferior vena cavae within the pericardium, which, when tethered, results in immediate emptying of the heart. The tolerance of the injured heart to this maneuver is limited, however, and should be used only for short periods if found to be necessary. This procedure can result in cardiopulmonary arrest and ventricular fibrillation, and appropriate plans should be made prior to caval occlusion should this happen. Atrial injuries can be repaired with running 2-0 Prolene. Ventricular wounds may be repaired while digitally occluding the laceration while placing a horizontal mattress stitch with a pledget surrounding the wound, usually with 2-0 Prolene. Repairing cardiac injuries resulting from gunshot wounds can be more challenging when compared with stab wounds, since they tend to have associated blast defects, which can make repair difficult. The repair of ventricular wounds adjacent to or involving coronary arteries can be challenging. If the coronary artery is injured itself but is quite distal (e.g., distal 1/3 of the left anterior descending artery), simple ligation can be done without serious consequences. However, if the injury is more proximal than this, ligation of the injury with distal bypass using a segment of saphenous vein or mammary artery is recommended. This can be done on or off cardiopulmonary bypass but usually requires the expertise of an experienced cardiac surgeon to perform. If the injury does not involve the coronary artery but is in close proximity, suturing of the injury may require placement of a horizontal U-stitch underneath the bed of the coronary artery, thereby closing the injury without compromising coronary blood flow. Patients who have sustained injury to their coronary artery that has already sustained irreversible myocardial damage may require intra-aortic balloon counterpulsation as part of their resuscitation.

Esophagus

Iatrogenic injuries to the esophagus are the most common, particularly those of iatrogenic esophageal perforation. Traumatic injury and Boerhaave's syndrome account for most of the rest.

Flexible endoscopy is associated with an extremely low risk of perforation. However, when flexible endoscopy is paired with a therapeutic intervention, such as dilatation or stent placement, the risk of perforation dramatically increases. As a result, most patients with iatrogenic perforation occur in patients undergoing therapeutic maneuvers in response to treating an underlying esophageal problem. Almost any form of esophageal instrumentation can cause perforation. Examples include nasogastric tube placement and performance of TEE. Common sites for perforation of the esophagus occur at areas of narrowing, such as in the pyriform fossa, at the aortic arch, near the carina, or at the lower esophageal junction. Perforation of an existing diverticulum can also occur, but this occurs rarely and is usually associated with blind passage of an endoscope when no antecedent barium swallow was obtained. The esophagus may also perforate at the site of a malignant stricture during forceful dilation or, more commonly, in the area of the esophagus just proximal to the stricture. Pneumatic dilatation

for achalasia carries an increased risk compared with routine esophageal dilatation, since this requires an uncontrolled tear of the lower esophageal sphincter to affect a myotomy. The risk of perforation with pneumatic balloon dilatation of the lower esophageal sphincter for achalasia ranges from 2% to 6%. Risk of perforation when performing esophageal dilation increases when dealing with long strictures or ones with poor blood supply, such as with radiation-induced strictures. Caustic strictures are usually transmural associated with extensive esophageal wall fibrosis and usually require repeated dilations, thereby multiplying the risk of perforation over time. Stent placement for the palliation of esophageal cancer is associated with a perforation rate of 7% to 15%. The incidence of perforation following sclerotherapy for esophageal varices is approximately 1% to 3% and typically occurs several days after the procedure, presumably due to tissue necrosis.

Patients who present with esophageal perforation usually complain of pain. Findings may include fever and subcutaneous or mediastinal air. Crepitus in the neck is relatively common following perforations of the cervical esophagus and can be detected on physical exam in approximately 60% of patients. Pleural effusions are present in more than 50% of patients with perforations of their thoracic esophagus. Radiologic studies are important in diagnosing patients with esophageal perforation. A plain chest radiograph may show subcutaneous emphysema, pneumomediastinum, pleural effusion, mediastinal air–fluid levels, or pneumothorax. Radiographic abnormalities can be found in as many as 90% of patients on plain film. Contrast studies are performed to confirm the diagnosis of perforation and to define the exact site. Water-soluble contrast agents such as Gastrografin have been the preferred agents of choice, at least initially. However, Gastrografin can cause severe pneumonitis if aspirated into the lungs, and its use may not demonstrate small leaks. Because of this, it is the authors' preference to use thin barium, because it is more inert and is better at detecting smaller leaks. CT scanning can be particularly helpful in showing mediastinal findings when the perforation has already sealed.

The optimal management of esophageal perforation is patient-specific and should take into account the clinical setting. This includes consideration of the patient's underlying disease process, the degree of sepsis, if any, the location of the perforation, and whether or not the perforation is contained. A nonoperative approach may be considered in patients with minimal symptoms and physical findings who do not appear septic and have a small, contained leak. Nonoperative management should include the use of broad-spectrum intravenous antibiotics and nothing to eat or drink by mouth (NPO). A nasogastric tube should be specifically avoided. There is no clear consensus as to generally how long a patient with a contained leak should be left NPO or how long intravenous antibiotics should be continued. However, clear liquids can usually be safely started within a few days and the diet advanced cautiously, especially when no further extravasation is seen on repeat contrast study.

Surgery should be performed if the patient appears septic, the leak freely communicates with either the peritoneal or thoracic cavities, or there is an associated mediastinal abscess. Primary repair can be done regardless of the timing of the injury, as long as the tissues appear healthy at the time of surgery. Drainage alone can be done for cervical perforations, especially if the perforation cannot be found at the time of operation, which is not infrequent. Primary repair with drainage is the preferred method when possible; however, if the esophageal tissues do not appear viable to hold sutures, then esophagectomy with proximal diversion may be necessary. It is important when primarily repairing the esophagus that the mucosal edges are defined, as the injury seen in the muscle layer is often only the "tip of the iceberg," and closure of the entire mucosal defect is necessary if adequate healing is to occur. As a general rule, esophageal reconstruction should not be done at the time of esophageal resection if the patient is septic, as it can usually be done at a later date once the patient heals and is beyond the acute event. In these cases, it is better to create an end cervical esophagostomy and oversew the gastric stump with the placement of enteral feeding catheters. If a cancer is perforated during instrumentation, then resection over primary repair is the preferred surgery of choice. Obviously, if the patient has widespread metastatic disease, then good clinical judgment needs to be used in deciding whether an operation should be done at all. Management of a perforation following achalasia dilatation should consist of primary closure of the perforation in addition to performing a surgical myotomy 180 degrees away from the site of perforation. An antireflux procedure consisting of a partial wrap to cover the area of repair can also be done to buttress the repair. This type of surgery is most commonly approached through the chest.

Spontaneous perforation of the esophagus usually can be related to forceful vomiting and retching. Boerhaave's syndrome has been reported following a variety of activities including straining, weightlifting, coughing, and emesis. The clinical features of Boerhaave's syndrome are similar to that of iatrogenic perforation, in that pain is the most common presenting symptom. Many patients with Boerhaave's syndrome do not have the classic antecedent history of forceful vomiting. The vast majority of these patients develop perforations in the distal esophagus on the left side, and the workup and treatment of patients with Boerhaave's syndrome is similar to those with iatrogenic perforations. Operation is usually indicated.

A Mallory-Weiss tear is a mucosal laceration, usually near the gastroesophageal junction, caused by forceful vomiting, and a hiatal hernia is found in more than 75% of patients. Most tears occur within 2 cm of the gastroesophageal junction on the lesser curvature of the stomach. Majority of the patients present with gastrointestinal bleeding. The classic presentation in up to 80% of patients is that of forceful emesis followed by hematemesis. Massive bleeding occurs in 10% of patients. Upper endoscopy usually confirms the diagnosis. The management of Mallory-Weiss tears is generally supportive, since the bleeding is usually self-limited. Occasionally gastric embolization may be necessary; surgical over-sewing of the tear is rarely necessary.

Esophageal injuries due to penetrating trauma are rare, with most series averaging only a handful [76–78]. They result most commonly from transmediastinal gunshot wounds. Asensio et al. reported their experience consisting of 43 penetrating esophageal injuries managed over a period of 6 years. Overall, 28 of their 32 survivors (88%) were managed by primary repair alone [79]. The overall mortality for their series was 26%. The authors also reported that these mortality figures were consistent with others reported in the literature, which have remained high and relatively stable approximately for the last 20 years, thus attesting to the critical nature of these injuries. Only Symbas et al. (48 cases) and Defore et al. (77 cases) have reported larger experiences but over much longer spans of time–15 and 22 years, respectively [76,77]. Penetrating esophageal injuries are not easily detected and require a high index of suspicion. Delay in diagnosis is associated with higher mortality. However, mortality can exceed 20% even for patients who are promptly diagnosed. Esophagoduodenoscopy (EGD) is a sensitive and safe diagnostic test for the detection of esophageal injury. A study by Flowers et al. showed that EGD had a sensitivity of 100%, a specificity of 96%, and an accuracy of 97% in detecting penetrating esophageal injuries [80]. There was no morbidity related to the examination, and, most importantly, no esophageal injuries were missed. The authors commented that the most significant potential weakness of flexible EGD for esophageal trauma is that it actually may

be too sensitive. EGD is most helpful in excluding esophageal injury in patients who require a surgical procedure for another injury. When found, prompt primary repair is the treatment of choice.

Caustic Injuries of the Esophagus

Caustic injuries of the esophagus can be very challenging to manage. They are most frequently due to suicide attempts in adults and accidental ingestion in children. The degree of injury to the esophagus is directly proportional to the amount of caustic substance ingested. Lye causes transmural liquefaction necrosis of the esophagus and therefore is most injurious. Diagnosis is usually from history, although patients attempting suicide may present with no history at all or, even worse, an inaccurate one. Examination of the buccal mucosa, mouth, tongue, and gums can often show chemical burns and suggest the diagnosis. Endoscopy should be performed to document the proximal extent of the injury only; there is no need to pass the endoscope further, since it may actually be harmful and potentially lead to perforation. Passage of an NGT is controversial, although it may actually help to "stent" the esophagus open and be associated with lower rates of stricture formation. Arterial blood gases should be obtained with particular attention paid to the base deficit, as this can be a marker for severity of injury. Signs and symptoms of perforation and sepsis should be carefully monitored. The patient should be made NPO, and broad spectrum intravenous antibiotics should be given. Steroids are controversial but have been associated with lower rates of stricture formation in some series [81,82]. Intravenous fluids should be given and consideration given to performing esophagectomy, if signs of perforation and mediastinal sepsis are present. Intra-abdominal perforations can also occur, as well as injury to surrounding structures (e.g., spleen, colon). If esophageal resection becomes clinically indicated due to sepsis, immediate reconstruction is ill-advised. Esophagectomy can be performed either transhiatally or transthoracically, with creation of an end cervical esophagostomy. Intra-abdominal feeding tubes should be placed for enteral access. Delayed reconstruction can then be performed electively once the sepsis clears and the patient heals, usually several months later. Late stricture formation is common and can be difficult to manage. In addition, the pharyngeal phase of swallowing can be affected, leading to debilitating problems with speech and swallowing. It is not uncommon to require serial dilations or even late esophagectomy if stricture formation develops. It typically involves long segments of the esophagus and is panmural in depth, often making dilation impossible or at best marginally effective. Overall prognosis is variable depending on the degree of injury.

Thoracic Aortic Injury

Traumatic disruption of the thoracic aorta immediately leads to death in majority of the patients. These horizontal acceleration/deceleration injuries usually result from a disruption of the integrity of the aortic wall just distal to the ligamentum arteriosum. Patients fortunate enough to survive initial injury usually do so because the aortic adventitial tissues are able to tamponade the tear, thereby preventing fatal intrathoracic exsanguination. The risk of rupture is dependent on multiple factors, including the ability of the adventitial tissues to contain the leak, the patient's systemic blood pressure, and the size of the contained pseudoaneurysm.

The entire surgical treatment section is confusing and needs to be rewritten. It jumps back and forth to operate and then not operate. It can be summarized and your opinion then given.

While emergent operative repair of thoracic aortic tears had become the standard of care, after 1997 there has been emerging evidence that not all thoracic aortic tears should be treated equally. In addition, associated injuries such as pulmonary contusions, intracranial hemorrhage, and/or intra-abdominal hemorrhage (which are common in these patients) may take precedence over the aortic injury. In these cases, the aortic injury can be acutely managed medically and definitive treatment delayed, so long as certain criteria are met. With careful medical management (strict blood pressure control, minimization of dP/dT), it has been shown that many thoracic aortic injuries can undergo delayed repair, perhaps resulting in superior outcomes when compared with those patients undergoing emergent repair [83,84]. A recent prospective, observational study sponsored by the American Association for the Surgery of Trauma (AAST) looked at the subgroup of patients that underwent immediate repair versus those that underwent delayed repair [85]. Those patients that underwent delayed repair of stable thoracic aortic injury actually had improved survival regardless of the presence of major associated injuries, although their length of ICU stay was longer. It should be noted that patients with no major associated injuries who underwent delayed repair had a significantly higher complication rate when compared to those patients undergoing immediate repair. Although there has not been a randomized, controlled trial of early versus delayed repair, these results probably reflect selection bias. However, selection bias, which reflects the "art" of clinical treatment planning, should not be underscored when making decisions regarding these often multiply injured patients. In addition, successful nonoperative therapy of descending thoracic aortic injury has been reported [86]. Justification for nonoperative therapy includes favorable anatomy of the injury (contained, small injury, hemodynamic stability) as well as the presence of coexisting injuries, which would render the operative risk prohibitively high. These include patients with spinal cord injury that might make lateral decubitus positioning dangerous; patients with pulmonary contusions that may make single lung ventilation difficult; and patients with closed head injury, solid abdominal organ injury, or major fractures in which systemic heparinization would be ill-advised. One accepted method of operative repair is the "clamp-and-sew" technique, in which the proximal and distal aorta are simply clamped, thereby isolating the injury so that either primary repair or interposition grafting can be performed. Operative mortality is generally reported to be 10% to 20% in most series, with major morbidity including renal failure and paraplegia, which appears to increase with prolonged (i.e., >30 minutes) clamp times [87]. Another accepted method of operative repair utilizes bypass of the injured segment during repair, either with partial left heart bypass or with proximal to distal aortic shunt placement (i.e., Gott shunt). Partial left heart bypass (with cannulae in the left atrium and distal aorta) allows controlled off-loading of the left heart in addition to maintaining distal aortic perfusion, especially to the kidneys, that may decrease (but not negate) the incidence of paraplegia, especially when prolonged clamp times are anticipated. Since there has not been a randomized controlled trial comparing the two techniques, and there is no conclusive evidence that one technique is superior over the other in terms of outcome, both methods are acceptable, and their performance is usually based on surgeon preference. The need for operative repair, however, which was once considered the gold standard, is now coming into question. There have been many reports showing that endovascular stent grafting of selected patients may actually be superior to that of "mandatory" operative repair. A prospective, multicenter study sponsored by the AAST was recently published that clearly shows the early efficacy and safety of endovascular stent grafting in selected patients with traumatic thoracic aortic injuries [88]. The patients who underwent stent grafting

had a significantly lower mortality (adjusted odds ratio: 8.42; 95% CI: [2.76 to 25.69]; adjusted p value < 0.001) and fewer blood transfusions (adjusted mean difference: 4.98; 95% CI [0.14 to 9.82]; adjusted p value < 0.046) compared to those patients that underwent operative repair. In addition, among the patients with major extrathoracic injuries, a significantly higher mortality and pneumonia rate were found in the operative group (adjusted p values 0.04 and 0.03, respectively). The major drawback seen in patients undergoing stent grafting were device-related complications, which developed in 20% of the patients. Their conclusion was that stent grafting of thoracic aortic injuries is now more commonly chosen by surgeons as the preferred method of repair and is associated with significantly lower mortality but that there is a considerable risk of serious device-related complications.

CARDIOPULMONARY CRITICAL CARE

Overview

It is not uncommon for severely injured patients to require cardiac and/or pulmonary support. This may be independent of whether or not they have sustained direct thoracic trauma. Pharmacologic drug therapy may be required to sustain adequate cardiac output and maintain necessary end-organ perfusion. In severe cases, cardiac failure may require mechanical support in the form of intra-aortic balloon pump counterpulsation. Respiratory support may be provided simply with supplemental oxygen administration; however, intubation and mechanical ventilation may be required. Unique ventilatory strategies such as high frequency oscillatory ventilation are sometimes required. In extreme cases, extracorporeal membrane oxygenation (ECMO) can be used and is potentially life-saving in a certain subset of selected patients. Due to both the severity of injury as well as the need for ventilatory support, it is not unusual for these patients to develop acute lung injury as well as ventilator-associated pneumonia.

Pharmacologic Drug Therapy

Pharmacologic agents are usually used early in the treatment of cardiogenic shock. For an in depth discussion of this topic, readers are referred to Chapter 58–60. Perfusion of vital organs is dependent on adequate oxygen and nutrient delivery to the tissues. This delivery is dependent on an adequate blood pressure (perfusion pressure), cardiac output, and intravascular volume including hemoglobin. If cardiac output and perfusion is maintained and yet there is not adequate oxygen-carrying capacity (i.e., hemoglobin), oxygen delivery to the tissues will be limited. There continues to be controversy and debate regarding what is considered to be an adequate hemoglobin level. However, many centers now use a hemoglobin level of < 7 g per dL as a transfusion trigger for patients without evidence of ischemic cardiac disease, signs and symptoms of impaired tissue perfusion, shock, or ongoing blood loss [89].

In addition, intravascular volume status, especially in chronically ill patients, is sometimes confusing. In fact, only half of ICU patients with hemodynamic instability will actually respond to fluid loading with a significant increase in their cardiac output [90]. This is because it is sometimes difficult to assess clinically exactly where the patient's heart is working on the Frank-Starling curve. If it is on the initial rise of the curve, the stroke volume is highly and directly dependent on the preload, and administering fluid will result in an increase in stroke volume. In contrast, however, if the heart is working on the top, more flat (and possibly even declining) portion of the Frank-Starling curve, fluid administration will not increase stroke volume and may actually worsen heart failure and pulmonary edema and, therefore, oxygen delivery to the tissues. Passive leg raise, which auto-transfuses volume to the patient, may be a reliable and simple predictor of responsiveness to volume administration. Measurements of cardiac output and responsiveness to fluid challenges can be obtained through the use of traditional, invasive pulmonary arterial catheter monitoring or, more recently, through less invasive means, such as esophageal Doppler monitoring, pulse contour analysis, indicator dilution, thoracic bioimpedance, and partial nonrebreathing systems.

Intra-Aortic Balloon Pump

When pharmacologic treatment is inadequate and cardiogenic shock becomes refractory due to pump failure, mechanical devices may be indicated. One such device is the intra-aortic balloon pump (IABP). For an in depth discussion of this topic, readers are referred to Chapter 45.

Metabolic support of the critically ill patient is important. For an in depth discussion of this topic, readers are referred to Chapter 190.

Mechanical Ventilation

For a complete discussion of mechanical ventilatory support, readers are referred to Chapter xx.

EXTRACORPOREAL MEMBRANE OXYGENATION

In patients who fail standard ventilatory strategies, rescue modalities such as ECMO may be a life-saving alternative. ECMO provides oxygenation of blood outside of the body (hence its extracorporeal nature) by membrane oxygenators similar to those used in cardiopulmonary bypass circuits. It requires placement of catheters within the vascular tree that allows deoxygenated blood to be drained and delivered to the membrane oxygenators; it then allows oxygenated blood to be delivered back to the patient. A certain degree of heparinization is usually required to prevent clotting of both the bypass circuits as well as the oxygenators. Typically, a catheter is strategically placed to drain the venous system to maximize the increase in O_2 content that can be achieved, which provides inflow into the oxygenators, which then oxygenate the blood and sweep off the excess carbon dioxide. The blood is then transfused back into the arterial system (venoarterial ECMO) or venous system (venovenous ECMO) depending on the setup. Given the low pressure characteristics of the venous system as well as its overall easier accessibility, venovenous ECMO is becoming increasingly more common. In addition, with the advent of newer catheters, a single catheter can now be used for both inflow and outflow which can be placed into the jugular vein and positioned such that deoxygenated blood drains from the superior and inferior vena cava (outflow) to the oxygenator, which is then returned directly to the right atrium (inflow). There is generally some mixing of the oxygenated and deoxygenated blood, but this type of system obviates the needs to access the arterial system and is still quite effective at oxygenating blood.

Several recent articles have suggested the usefulness of ECMO in the surgical intensive care unit, but its exact role is yet to be determined [91–93].

Respiratory Complications

As a result of either primary lung contusion or from the treatment necessary to treat generalized traumatic injury (e.g., massive transfusions, mechanical ventilation, etc.), the lungs are susceptible to acute injury. Complications which can develop include transfusion related lung injury (TRALI), ventilator associated pneumonia (VAP), or ARDS. For an in depth discussion of these three complications, readers are referred to Chapters 47, 68, and 114.

SUMMARY

In summary, most thoracic trauma can be managed without surgery or, at most, with minimally invasive interventions. Multiply injured patients with thoracic injuries need to be comprehensively evaluated and their injuries prioritized and as a result, their successful care often requires a multidisciplinary approach. The treatment of thoracic injuries is evolving and requires a working knowledge of a number of both diagnostic and therapeutic modalities. As with almost all other traumatic injuries, the key to optimal treatment and outcome is dependent upon having a high index of suspicion for the injury and to identify it early. The ability to competently manage all aspects of a critically injured patient is also important in effecting a successful overall outcome.

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CHAPTER 165 ■ CRITICAL CARE OF THE PATIENT WITH ABDOMINAL TRAUMA

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In many ways the care of the abdominal trauma patient in the intensive care unit (ICU) is similar to that of other patients with abdominal pathology and as such should be familiar to the intensivists. This chapter will focus on those common aspects of abdominal trauma care that are sufficiently rare in the nontrauma patients that many intensivists may have little experience in recognizing or managing them.

One possible origin of the word abdomen is the Latin *abdere*, meaning to conceal. Few areas of the human body are as difficult to assess following injury or to monitor subsequently as is the abdomen. Much of the morbidity and mortality due to abdominal injury results from delay in recognizing conditions that are easily corrected once identified. Improvements in resuscitation and modern high-speed imaging have done much to

improve the initial management of abdominal trauma. However, after the patient reaches the ICU, the ability to follow changes occurring within the abdomen deteriorates substantially.

ICU ADMISSION

In previous years, trauma patients arriving in the ICU were assumed to have had their injuries identified and repaired prior to arrival, and therefore the ICU was for monitoring and support. Today the ICU plays a larger role in the care of trauma patients. Many patients with abdominal injuries are managed nonoperatively. Many operated patients have their surgery performed in stages with interposed additional resuscitation in the ICU. The management of the abdominal injuries is now known to have an impact on the function of remote organs such as the lung and the brain, thus there must be close cooperation and shared knowledge between the trauma surgeon and the intensivist.

Trauma surgeons have traditionally divided injured patients into those injured by penetrating mechanisms such as gunshot wounds or stab wounds and those injured by blunt mechanisms such as car crashes and falls. Clearly, some patients manifest components of both types of injury but this classification has been a useful way to divide and compare trauma patients for years. Despite this long tradition and its advantages, for our purposes, it may be more useful to think of abdominal trauma patients coming into the ICU as those who have been operated upon and those who have not.

Operative trauma patients will have had a laparotomy and their injuries should have been defined. There will be a tendency for the intensivist to consider them identical to the elective general surgical patient who has undergone a comparable operation. While there are certainly areas of commonality, there are critical differences that must be considered. The elective general surgical patient will not, in all probability, have had a period of shock preoperatively and intraoperatively. The general surgical patient will usually have only a single acute problem unlike the trauma patient who may have sustained multiple organ system injuries including more than one in the abdomen. These differences often lead to management problems and complications that would not be expected in the general surgical patient and to more frequent complications such as infections.

Many blunt injury patients and some penetrating injury patients are now managed with the intention of not operating on them. This approach has grown out of the recognition that many trauma laparotomies are nontherapeutic as opposed to negative. For example, a laparotomy for hemoperitoneum that identifies a small liver laceration and a minor tear in the mesentery is certainly not a negative laparotomy but if both injuries have stopped bleeding spontaneously, it is difficult to argue that the surgery was therapeutic. Nontherapeutic laparotomies are not without consequences. They are painful, they expose the patient to early risks of wound infection, pneumonia, DVT, and so on, and the late risks of incisional hernia and bowel obstruction [1,2]. These risks are statistically small but significant. However, avoiding them by attempting to manage injured patients nonoperatively is only sensible if it can be done without a significant increase in the incidence of missed injures that do need intervention.

NONOPERATIVE MANAGEMENT

Nonoperative management of intra-abdominal injury is so widely practiced that trauma surgeons often feel they have to attempt nonoperative management or justify why they want to operate on a splenic or liver laceration. Nonoperative management of abdominal organ injury is appropriate only for hemodynamically stable patients whose injuries are identified by imaging. Hemodynamic stability is a nonspecific state but generally implies a systolic blood pressure more than 90 mm Hg without the rapid infusion of fluid, blood products, or the use of pressors. Significant tachycardia or metabolic acidosis if present would also preclude a state of hemodynamic stability. Other factors beyond hemodynamic stability also deserve consideration before a decision to attempt nonoperative management is made. Are there multiple injuries that may increase the risk of failure? Are there medical conditions such as portal hypertension or the use of anticoagulants? Patients with severe head injuries or ischemic heart disease are often considered a high operative risk but a failure of nonoperative management also poses a high risk mortality. Other factors also play a role. Older patients are less likely to undergo successful nonoperative management [3,4].

As imaging has improved, trauma surgeons have been given a more precise determination of the anatomic location and severity of the injury prior to deciding whether or not to operate. This information has allowed the construction of a number of models intended to predict the success of nonoperative management [5]. CT based injury grading systems do show a positive correlation with clinical outcomes but like most scoring systems work better for analyzing populations than for predicting the outcome of individual patients [6,7].

One of the most useful CT findings is the presence of extravasated vascular contrast. This contrast blush usually represents either active bleeding or a pseudoaneurysm of a parenchymal artery. Such patients have a higher probability of failing nonoperative management. Angiographic embolization of the injured vessel may help to restore them to the nonoperative pathway [8].

Spleen

The current practice of managing splenic injury without surgery grew out of a desire to protect children from postsplenectomy sepsis. It was discovered that most children's injured spleens stop bleeding without surgery. This practice was gradually extended into the adult population where the results are not as good but still approach 80% among stable patients. Multiple studies have been conducted in an attempt to more accurately predict which patients will succeed and which will fail attempts at nonoperative management. They have focused on combinations of patient factors such as age and vital signs and CT factors such as contrast blush and depth of laceration [3,4,6]. Failure of nonoperative management not only delays effective therapy and consumes resources, but patients who fail attempted nonoperative management have greater morbidity and mortality [8]. Advanced age, portal hypertension, and coagulopathy increase the probability of the failure of nonoperative management.

The nonoperative management of a ruptured spleen must be a joint effort between the surgical team and the ICU team. The parameters that will default the patient to the operative pathway should be agreed upon in advance between those who will be monitoring and supporting and those who will operate. In general, any indication of hemodynamic instability should lead to immediate surgery and splenectomy. If the patient experiences a steadily falling hemoglobin level but never manifests any change in vital signs, there should be prior agreement regarding the number of units of packed red blood cells (PRBCs) to be transfused prior to resorting to surgery. The absolute number will vary with the estimated operative risk, other factors predicting success or failure, and the patient's preference but should rarely exceed four units of PRBCs for an isolated splenic injury.

Splenic embolization may be an option in some facilities for those patients whose CT demonstrates a contrast blush within the spleen. If embolization is to be utilized, it should

be performed by a team that is readily available and has demonstrated success with the procedure.

Patients admitted to the ICU for nonoperative management of an isolated splenic injury should receive their planned immunizations including pneumococcal, meningococcal, and Hemophilus influenza vaccine since there is evidence that these vaccines are more effective with the spleen *in situ* [9].

When the splenic injury is successfully managed nonoperatively, there are still potential complications. Delayed bleeding of a lacerated spleen is a well-recognized complication of splenic injury. Many programs will follow elaborate algorithms specifying when patients may increase physical activity and participate in activities such as physical therapy since such activity is perceived to play a role in delayed rupture. However, there is no convincing evidence that, short of avoiding a blow to the flank, one regimen is superior to another. Pain associated with either capsular distention or infracted splenic tissue may eventually necessitate splenectomy, particularly if the spleen is embolized. The other major complication is an infection involving the injured splenic parenchyma or the perisplenic hematoma resulting in either splenic or subphrenic abscess [10]. Unexplained fever, leukocytosis, pleural effusion, or hiccoughs should necessitate an abdominal CT scan looking for evidence of infection. Most such infections can be effectively treated with antibiotics and percutaneous drainage but failure to respond promptly should result in exploration, evacuation of the infected hematoma, and splenectomy.

Liver

The other commonly injured organ in blunt abdominal trauma is the liver. The injured liver differs from the injured spleen in two significant ways. First, removal of the injured organ is not a treatment option. Second, the liver secretes bile directly into the GI tract so that liver injuries have a more complex range of complications including bile leak, hemobilia, obstructive jaundice, and so on. While the surgical options differ from the spleen, the decision to operate should be based on similar considerations. The first criterion for successful nonoperative management is hemodynamic stability. A patient who does not meet this condition should be taken to the OR, explored, and if necessary, packed, since the organ cannot be totally removed. Experienced trauma or hepatic surgeons will more often be able to perform a definitive procedure initially but the lack of such surgeons should rarely lead to an attempt to manage an unstable patient nonoperatively. Perihepatic packing followed by either angiography with embolization, reexploration when more experienced personnel are available, or transfer to a more capable facility are all preferable to attempting to manage an unstable patient nonoperatively. Conversely, surgical exploration in the face of hemodynamic stability by an inexperienced team is a recipe for disaster and should be avoided.

Patients with solitary liver injuries admitted to the ICU for nonoperative management should first be evaluated for hemodynamic stability and if stable should next be evaluated to determine whether they are likely to benefit from angiography and embolization. Patients with contrast extravasation or severe lacerations extending deep into the hepatic parenchyma are candidates for angiography with embolization. Liver injuries in the face of cirrhosis, portal hypertension, or coagulopathy are much more likely to fail nonoperative management than comparable injuries lacking these comorbidities.

Complications of nonoperative management are primarily the result of bleeding, infection, bile leak, hepatic necrosis, and jaundice. Delayed bleeding from a liver laceration may occur but sudden unrelenting hemorrhage from the liver necessitating emergency surgery is rare beyond 24 hours postinjury. Steadily falling hemoglobin levels in an otherwise stable patient are an indication for either repeat CT scanning to verify that the bleeding is coming from the liver or angiography in an attempt to identify a vessel suitable for embolization.

Bile leaks from the injured liver may result in either contained collections known as bilomas or more diffuse biliary ascites. Bilomas may cause compression of adjacent structures producing jaundice or gastric outlet obstruction in the subhepatic location but the more common problem resulting from bile leak is secondary infection. Small bile leaks occur commonly after liver injury but most are of no clinical significance. Elevated liver function tests after liver injury are an indication for hepatobiliary imaging, or hepatobiliary iminodiacetic acid (HIDA) scan to evaluate for a bile leak. Signs and symptoms of infection are usually better evaluated with a CT scan. Patients in whom a fluid collection is identified should undergo percutaneous drainage if they show evidence of infection. If the drained fluid shows a bilirubin level significantly above that of serum, the patient should then undergo HIDA scanning. Most such bile leaks will seal with adequate drainage of the fluid collection. If bilious drainage persists, they should be evaluated for endoscopic retrograde cholangiopancreatogram (ERCP) with stent placement.

High fevers, often exceeding 39°C, may be seen in patients with liver injury typically beginning 48 to 72 hours postinjury. These fevers have been blamed on atelectatic lung immediately above the diaphragm or on areas of hepatic necrosis. Solid evidence to firmly establish the cause of such fevers is not available. Patients who sustain severe liver injuries but remain hemodynamically stable may nonetheless harbor significant areas of devitalized liver. In the vast majority, this necrotic liver does not require resection. However, if the necrotic liver becomes infected or if the patient deteriorates, resectional debridement of the necrotic material may be necessary.

Hemobilia is a rare complication of hepatic injury. The classic triad of gastrointestinal hemorrhage, jaundice, and right upper quadrant pain should suggest the diagnosis. It may present anytime from the first few days postinjury to months later. Diagnosis is often difficult and delayed. The bleeding is usually intermittent so that diagnostic endoscopy may demonstrate no source for the bleeding. Any patient with a history of hepatic trauma, either immediate or more remote, who has evidence of unexplained gastrointestinal hemorrhage, should undergo diagnostic angiography coupled with therapeutic embolization if a hepatic pseudoaneurysm is identified [11].

Kidney

Renal injury is most often the result of blunt trauma and frequently occurs in conjunction with other injuries. Right renal injury most frequently occurs in conjunction with hepatic injury and left renal injury in conjunction with splenic injury. Renal injury is almost always associated with hematuria but the severity of the hematuria and the degree of the renal injury are often discordant. Gross hematuria may appear dramatic but most renal bleeding diminishes spontaneously within a few hours of injury. Even impressive perinephric hematomas on CT often have little impact on management decisions [12,13].

The kidney has two possible responses to injury that may require monitoring and or intervention, contrast extravasation from bleeding or a urine leak. Rarely will the hemodynamically stable patient continue to bleed from a lacerated kidney. In such cases, the management is similar to the other solid organs with appropriate imaging to confirm the source of bleeding followed either by embolization or surgical exploration. Usually, extravasation of urine from an injured kidney will resolve spontaneously [12,13]. Extravasated contrast that is confined within Gerota's fascia does not mandate immediate intervention since it will frequently resolve spontaneously or respond to minimally invasive methods. Leakage of urine as demonstrated by delayed contrast extravasation outside of Gerota's

fascia may still resolve but is more likely to benefit from percutaneous drainage of the renal collecting structures. Persistent urine leakage often indicates ureteral obstruction from either urinoma or retroperitoneal hematoma and may benefit from ureteral stenting.

Renal vascular injury is most often recognized on CT with intravenous contrast as an area of renal parenchyma that does not enhance. This injury may involve a single segment of the kidney or the entire kidney. Although gross hematuria may occur, it is typically of very short duration and may be absent altogether. Microscopic hematuria is virtually always present. The arterial injury may be either complete disruption or thrombosis. However, even with complete disruption, significant hemorrhage into the retroperitoneum is rare. Revascularization is rarely of benefit since in most cases, the time required for diagnosis, surgical exposure, and repair is beyond the warm ischemia tolerance of the kidney. Segmental infarction or even infarction of one entire kidney is usually well tolerated if the other kidney is healthy. Sequelae such as pain, abscess, bleeding, or hypertension are rare. Compression of the kidney by either hematoma or urinoma with subsequent renovascular hypertension (Page kidney) is extremely rare.

Pancreas

Blunt pancreatic injury is typically the result of high energy impact to the epigastrium. Because the pancreas is well protected by the costal margin and is located deep in the retroperitoneum, isolated pancreatic injury is rare. Physical findings are usually minimal and laboratory and imaging studies are often nondiagnostic. As a result of the difficulty in early diagnosis, isolated pancreatic injuries are rarely the cause of ICU admission. However, patients with injuries to liver, spleen, or kidney may show some abnormality associated with the pancreas during the course of their nonoperative management. Elevations in serum amylase or nonspecific findings on CT scan will not usually change the plan to manage the patient nonoperatively. However, it is important to insure that the duodenum is not injured. Duodenal perforation and pancreatic injury are often difficult to differentiate.

Serum amylase values are commonly relied upon to evaluate the pancreas following injury but the sensitivity and specificity of serum amylase leaves much to be desired in the early postinjury period. Serum amylase values determined within 3 hours of injury appear to be particularly unreliable [14]. A normal serum amylase value later in the patient's course appears reliable in excluding a significant pancreatic injury. An elevated serum amylase value is much less specific, particularly in the setting of head injury [15]. Certainly, an elevated amylase should raise the level of suspicion sufficiently to pursue further evaluation of the pancreas. CT findings may also be less than diagnostic. Suggestive CT findings include visualization of a fracture of the pancreas, intrapancreatic hematoma, fluid in the lesser sac, retroperitoneal hematoma or fluid, and so on. As with the serum amylase value, CT scans obtained very early postinjury may be falsely negative [16]. These findings should not be interpreted as suggesting that a delayed work up is the preferred method but rather these results emphasize the importance of repeating both the amylase and if necessary the CT scan in cases where suspicion of pancreatic injury remains.

The critical determinant of whether pancreatic injuries can be managed nonoperatively is the integrity of the pancreatic duct. If pancreatic ductal disruption is present, distal resection or internal drainage produces much less morbidity than simple drainage or noninvasive management [17]. If no definitive reason for surgical exploration exists but there is reason to suspect or diagnose a pancreatic injury, it is imperative to evaluate the ductal integrity. If there is any suggestion of instability or peritoneal signs, this should be performed at the time of abdominal exploration. Otherwise, the patient may be a candidate for magnetic resonance cholangiopancreatography (MRCP) or even the more invasive ERCP. Delay in diagnosing and providing definitive therapy for a ductal injury may have devastating consequences.

Pelvic Fracture

Pelvic fractures represent the exception to the rule that nonoperative management is only suitable for hemodynamically stable patients. Surgical exploration of the pelvic hematoma is usually not an effective way to control the hemorrhage from a pelvic fracture. Thus, once other sources of bleeding have been excluded, even hemodynamically unstable patients may be managed in the ICU.

Although the focus of pelvic fracture management in the ICU is on dealing with the blood loss into the pelvis, it is important not to lose sight of the abdominal distention, and limitation of diaphragmatic excursion that can occur. Patients with significant bleeding into the pelvis should be monitored very carefully for respiratory compromise. This is particularly true during any transport out of the ICU to sites such as radiology. If there is any doubt of the patient's ability to maintain adequate spontaneous ventilation, the airway should be secured electively and the patient placed on positive pressure ventilation.

A great deal of force is required to fracture the pelvis. Therefore, it is not surprising that associated injuries are common. Abdominal injuries and lower extremity fractures are both common in patients with pelvic fractures. These associated injuries often make it difficult to ascertain the site of bleeding. It is essential to evaluate the CT scan for the presence of intraperitoneal blood and solid organ injury as well as the size of the pelvic hematoma and the type of pelvic fracture. Lower extremities should be examined and x-rayed if any question exists of fracture. The type and location of pelvic fracture can provide valuable information regarding the likelihood of bleeding. Fractures or ligamentous disruptions of the posterior pelvis are more likely to be associated with severe hemorrhage than anterior fractures, acetabular fractures, or fractures of the iliac wing [18]. So called vertical shear fractures of the pelvis are particularly likely to be associated with arterial bleeding from the superior gluteal artery or other branches of the internal iliac system [19].

It is imperative to carefully examine the perineum for lacerations that may suggest an open pelvic fracture. This includes a careful rectal examination and a vaginal examination for females. If there is any indication of blood in the rectum or vagina, an endoscopic or speculum examination is required. An adequate examination is likely to be extremely painful with the pelvic fracture and often fractured lower extremities that make positioning very difficult. The examination should not be compromised even if it requires airway control and deep sedation. It may also require the assistance of the orthopedist to minimize fracture movement during the examination. The consequences of missing an open pelvic fracture may be disastrous.

Imaging of the abdomen and pelvis can provide a tremendous amount of information to assist the physician in deciding whether the ongoing blood loss is coming from the pelvic fracture or the abdominal viscera. However, the old adage, "Death begins in radiology" remains true today. Patients with pelvic fractures are at risk for both massive hemorrhage and the respiratory compromise often associated with a massively distended abdomen. They should be accompanied by personnel capable of dealing with these problems whenever they leave the ICU.

If there is a significant increase in the free blood within the peritoneal cavity on repeat focused assessment with sonography for trauma (FAST) examination or repeat CT scan, it may be impossible to be certain whether the bleeding is coming from a decompressed pelvic hematoma or from an abdominal site. In

such cases, the patient should be explored. If the only source of the blood loss is found to be the pelvis, the hematoma should be left intact, the abdomen closed, and the patient's pelvic fracture managed in the appropriate manner based on the fracture and hematoma. If the pelvic hematoma is significantly disrupted the only option is packing of the pelvis to achieve tamponade of the bleeding. If the patient has not already been studied angiographically, this should also be completed urgently.

Once the bleeding has been determined to be arising from the pelvic fracture, the first priority as with any other trauma patient, is the maintenance of intravascular volume, hemoglobin concentration, and the correction of coagulation abnormalities. The blood bank should be notified to keep adequate quantities of PRBCs, plasma, and platelets available. The fracture should be stabilized since continued movement of fracture fragments leads to further bleeding. This may be accomplished by one or more of several techniques depending on the fracture and the pelvic geometry [20]. Close consultation between the orthopedic trauma service, the general surgical trauma service, and the ICU is vital. If the pelvic volume is enlarged by the expanding hematoma, every effort should be made to reduce the volume toward normal thus compressing the hematoma. This may be accomplished by external fixation devices or some form of pelvic binder [21]. If stabilization of the fracture and compression do not promptly control the hemorrhage, the patient should undergo angiography of the pelvis with the plan to embolize any bleeding vessels arising from the internal iliac system and stent any injury to the common or external iliac systems. Severe vertical shear pelvic fractures even when managed appropriately may frequently require up to 20 units of PRBCs and the accompanying plasma and platelets. If all the other options have been exhausted or are unavailable, consideration may be give to retroperitoneal exploration for the purpose of packing or ligation of the internal iliac vessels [22].

The complications of pelvic fracture are primarily the result of massive blood loss and transfusion and of increased intra-abdominal pressure from the hematoma leading to respiratory compromise, renal failure, and acidosis that will be discussed in more detail under the abdominal compartment syndrome.

Other

Nonoperative management of abdominal injuries is usually confined to the so-called solid organs. There are two exceptions to this generalization. Intramural hematoma of the duodenum and extraperitoneal rupture of the urinary bladder are commonly and effectively managed nonoperatively.

Blunt duodenal injuries are primarily the result of a direct blow to the epigastrium such as from the steering wheel or seat belt in a motor vehicle crash. In the American Association for the Surgery of Trauma (AAST) grading system, duodenal hematomas are either Grade I or II injuries depending on the length of the duodenum involved [23]. This injury is commonly thought of as an injury of childhood, particularly from child abuse, but it does occur in adults as well. Symptoms, when present, will be those of gastric outlet obstruction. Diagnosis is made from a CT scan with oral contrast or an upper GI study. The patient should be carefully evaluated for any evidence of a concomitant pancreatic injury. Such patients are best managed conservatively if there are no associated injuries. Gastric decompression and nutrition support should be employed and the patient reevaluated radiographically at weekly intervals. The obstruction usually resolves in 2 to 3 weeks. If it has not resolved in this time period, surgical exploration for possible stricture repair should be considered.

Approximately 80% of bladder injuries occur in the setting of pelvic fracture although only about 5% of pelvic fractures are associated with bladder injuries [24]. Bladder injuries are most often extraperitoneal and result from perforation of the bladder by bone fragments from fractures of the parasymphyseal pelvis. This may occur even though the final position of the bone fragments as demonstrated on radiographs does not appear near the bladder. Radiographs taken in the hospital do not reflect the location of the bone fragments at the point of maximal displacement during the crash. Bladder injury is also suggested by the inability to void or the incomplete return of catheter irrigation into the bladder. Any pelvic fracture associated with gross hematuria requires imaging of the bladder. Diagnosis requires retrograde contrast injection into the bladder with images taken in both the AP and lateral views and postvoiding. CT scan with IV contrast can give a high quality image of the bladder if the Foley catheter is clamped early enough to produce distention of the bladder or extravasation. Extraperitoneal rupture is demonstrated by the leakage of contrast with the contrast confined to the area around the base of the bladder. Extraperitoneal injuries typically resolve with simple catheterization in 7 to 10 days. Prior to removal of the catheter, a repeat cystogram should be obtained to confirm closure. Persistent extravasation often requires surgical repair of the bladder.

PENETRATING INJURY

The majority of the patients admitted to the ICU for nonoperative management will have sustained blunt trauma but in some institutions selected cases of penetrating trauma may be admitted to the ICU for close monitoring. As with blunt trauma, the fundamental requirement for nonoperative management is hemodynamic stability and the absence of peritonitis. Any change toward hemodynamic instability or the development of peritoneal signs should mandate exploration.

Stab wounds are much more likely to be monitored nonoperatively than gunshot wounds. This is because knife wounds not only have a lower incidence of actually penetrating the posterior abdominal fascia but even if penetration occurs, they have a lower risk of producing an injury that requires repair. In addition to frequent serial abdominal examination and serial laboratory studies, any of the several techniques may be employed in an effort to determine the need for subsequent surgical exploration. These may include local wound exploration looking for evidence of posterior fascial penetration, diagnostic peritoneal lavage, FAST examination, or CT scan [25]. These modalities will most commonly have been employed in the emergency department but the intensivist should be familiar with the results and the possibility that they may need to be repeated while the patient is in the ICU.

Gunshot wounds are rarely managed nonoperatively if they enter the peritoneal cavity because of the much higher probability of visceral, particularly hollow viscus, injury. However, the advent of high-resolution CT imaging is now allowing the nonoperative management of highly selected abdominal gunshot wounds. These cases are primarily patients in whom the entire tract of the missile appears to be visible within the liver [26] and who are considered high-risk operative candidates either because of multiple previous abdominal operations or serious medical comorbidities. Such patients should be monitored in a manner similar to blunt trauma patients with the added concern that hollow viscus injury is still a concern.

MISSED INJURIES

No matter how careful the initial evaluation of the trauma patient, almost all series report a 10% to 20% incidence of missed injuries that are discovered in a delayed fashion [27]. Most of these are minor fractures discovered as the patient begins to increase activity and reports pain. The consequences of these delays in diagnosis are generally minor. However, a delay in

the diagnosis of a hollow viscus injury may have serious repercussions. Avoiding delays in diagnosis requires the cooperation of the entire trauma team including emergency physicians, surgeons, intensivists, and radiologists. The initial examination should be complete and take into account mechanism of injury, bruises and abrasions, patient complaints, and laboratory and radiographic studies. In spite of such a thorough evaluation, additional information will often become available over the first 24 to 48 hours. Bruises, abrasions, seat belt marks, and so on will often be more apparent the next day. Laboratory and even imaging studies are less sensitive when the patient arrives at the trauma center within an hour or two of injury. Although not a formal component of the Advanced Trauma Life Support (ATLS) course, these facts have led many trauma centers to institute a formal tertiary survey at 24 of injury after admission [28]. During the tertiary survey, the patient should be carefully reexamined looking for new evidence of traumatic injury, such as seat belt abrasions that were not apparent initially. The abdomen should be reevaluated for evidence of peritoneal irritation. Radiographs should be reexamined and compared with the formal radiology interpretation. Such tertiary surveys are even more important when the patient is initially unstable and examiners may be distracted by urgency of the situation. Although there is no evidence to suggest the routine use of repeat imaging, a repeat FAST or even CT scan should be obtained if there is any question of change in the initial evaluation. Some injuries such as pancreatic or duodenal injury may be more apparent on a CT scan performed at 24 hours postinjury than on the initial scan. Even the sensitivity of procedures such as peritoneal lavage increases with time.

Bowel

The major concern with missed abdominal injury is the possibility of a missed bowel perforation. A patient who has a bowel perforation with significant spillage will manifest signs of peritoneal irritation quickly if the examination is not compromised by head injury, intoxication, or distracting injuries. Small perforations with minimal spillage may show little in the way of physical findings for several hours. Such injuries are often missed on preoperative imaging and can be easily missed at the time of surgical exploration. Both the patient arriving in the ICU with negative abdominal imaging studies and the patient admitted following abdominal exploration must be reevaluated for bowel injury if they show signs of intra-abdominal infection, unexplained sepsis, prolonged ileus, glucose intolerance, and so on.

With typical 20–20 hindsight it is the knee-jerk reaction to ask how an injury could have been missed at the time of surgical exploration but unfortunately it is easy to be misled at the time of exploration. Urgency of hemorrhage control may lead to oversight. An apparently straight missile tract may not have been so straight. Bowel may have been in a different configuration at the time of penetration. Areas that did not appear injured such as the retroperitoneum may not have been explored. Areas of bowel injury that did not appear transmural may have been deeper than was realized. It is incumbent upon the operating surgeon to explore the abdomen thoroughly but in spite of this, injuries will at times be missed. Neither the operating surgeon nor the intensivist caring for the patient in the ICU should dismiss the possibility if the patient is not recovering as anticipated.

Patients admitted to the ICU for planned nonoperative management are at particular risk. The sensitivity and specificity of CT scanning leave much to be desired for hollow viscus injury [29]. Spillage of oral contrast into the peritoneal cavity is a relatively infrequent finding, even with significant bowel injury. The segmental ileus resulting from the injury tends to obstruct the flow of contrast proximal to the site of injury. Free air may be demonstrated but its absence certainly cannot exclude bowel injury. An area of localized thickening of the bowel wall is suggestive of injury, while a diffuse thickening is more compatible with either excess fluid administration or poor perfusion. The CT finding that causes the most confusion is free fluid in the peritoneal cavity without evidence of a solid organ injury to account for the bleeding. Some consider this sufficient evidence for exploration, while others disagree [30].

Injuries of the mesentery are usually detected on CT due to the associated hemoperitoneum and mesenteric hematoma. It is much more difficult on CT to recognize which mesenteric rents will be associated with intestinal ischemia and delayed perforation. Any mesenteric injury that is not explored surgically must be monitored carefully in the postinjury period to allow the recognition of ischemic bowel prior to perforation. The development of a rising WBC, glucose intolerance, persistent ileus, or signs of peritoneal irritation should prompt investigation if not exploration.

Even bowel injuries that are transmural may show little in the way of physical findings for several days. The localized area of ileus associated with the injury, the diffuse ileus from injury, edema, and narcotic administration may limit the degree of spillage. This same process will often prevent the spillage of CT contrast delaying the diagnosis initially. The physician caring for such patients should remember that an ileus is not a diagnosis but a sign. If it persists, it is important for the intensivist to search for the cause. This may require repeat imaging.

Pancreas

Injuries to the pancreas are easy to miss. CT scans and serum amylase determinations performed in the first 3 hours after injury may be normal [14,16]. The accuracy of both tests increases with time. With isolated pancreatic injury, a missed injury is most likely to result in the leakage of pancreatic secretions but since the enzymes are not activated this is usually well tolerated. Most often the fluid is confined to the lesser sac and unless it becomes infected will resolve spontaneously assuming it does not arise from a major ductal injury. If a major duct is injured the fluid may eventually organize into a pseudocyst requiring internal drainage. Less frequent is the development of pancreatic ascites.

Renal Collecting System

Injuries to the renal collecting system including the renal pelvis, ureters, and bladder may present as a rising blood urea nitrogen (BUN) without obvious explanation, as new onset ascites without evidence of portal hypertension, as drainage of serosanguineous fluid from the incision, or as a mass in the flank or pelvis. In the presence of urinary tract infection, this may lead to the serious complication of an infected pelvic hematoma. The diagnosis is usually not difficult as long as a urine leak is considered. CT with intravenous contrast will usually establish the diagnosis. Any unexplained fluid collection in the abdomen that is aspirated should be analyzed for creatinine and compared to a simultaneous serum level. Most injuries that are diagnosed late can be managed with decompression or stenting although complete transection of a ureter will require reimplantation.

Solid Organs

The probability of missing a solid organ injury if the patient has received a CT scan with intravenous contrast is low. Such scans identify approximately 98% of solid organ injuries. However, if the patient does not receive such a scan on the basis of what

is perceived to be a normal physical examination with or without a FAST examination, such errors are then more likely. As already discussed, there are many reasons for an erroneous physical examination. Blood in the peritoneal cavity does not always produce peritoneal irritation immediately. There may be associated intoxication, head injury, or distracting injuries. FAST examinations are intended to assess the quantity of free fluid in the abdomen, not the integrity of the organs. Many liver, spleen, or kidney lacerations produce little or no free fluid on initial examination. Patients admitted to the ICU without abdominal CT scanning or if no contrast was employed should be monitored with both vital signs and serial laboratory studies at a frequency appropriate for their overall condition. Any unexplained deterioration in either should prompt an immediate FAST examination if the patient is unstable and both a FAST and a CT if the patient is sufficiently stable to transport to radiology.

ABDOMINAL COMPARTMENT SYNDROME

The abdominal compartment syndrome (ACS) is a well-recognized complication of abdominal trauma but despite widespread familiarity among intensivists, the diagnosis is often delayed or missed all together. There are reports in the medical literature dating back to the 1800s describing the deleterious results of intra-abdominal hypertension but the clinical diagnosis was imprecise, unreliable, and infrequently made. With the report by Kron et al. [31] in the 1980s describing the indirect measurement of intra-abdominal pressure by the bladder, the bedside diagnosis became more precise and easily quantifiable. The pathophysiology and treatment became well defined. Abdominal compartment syndrome assumed even greater importance with the widespread use of damage control surgical techniques. A complete review of abdominal compartment syndrome is presented in Chapter 156, including current definitions, pathophysiology, systemic consequences, measuring techniques, and management. We discuss it briefly here as it relates specifically to abdominal trauma.

Pathophysiology

The fundamental physiology of ACS does not differ from any other compartment syndrome, whether in the leg, the cranium, or elsewhere. It may occur as a result of bleeding, edema, or packing within the abdomen; referred to as primary compartment syndrome, or as a result of ischemia-reperfusion and capillary leak associated with other disease processes such as major burns or systemic sepsis. This is referred to as secondary compartment syndrome. Pressure within the relatively rigid abdominal compartment increases until the perfusion pressure is inadequate to meet the oxygen and nutrient needs of the tissues within the compartment.

$$APP = MAP - IAP \quad (1)$$

where APP, abdominal perfusion pressure; MAP, mean arterial pressure; IAP, intra-abdominal pressure.

However, unlike the more rigid bony cranium, the abdominal compartment is only semirigid. As IAP increases, the abdomen distends and a portion of the pressure is transmitted to the surrounding structures. To have a reproducible diagnosis we must standardize the measurement technique. While the most direct technique involves the insertion of a fluid filled catheter directly into the peritoneal cavity, this is often not practical in injured patients. The accepted clinical technique is an indirect measurement by the bladder although IAP can also be measured through the stomach or the inferior vena cava (IVC).

TABLE 165.1

GRADING SCALE FOR INTRA-ABDOMINAL HYPERTENSION [32]

Grade	IAP (mm Hg)	Recommendations
I	10–15	Monitor, maintain intravascular volume
II	16–25	Sedation, muscle relaxants, increase cardiac output, often with volume expansion
III	26–35	Decompression
IV	> 35	Decompression and reexploration, especially if organ dysfunction is present

Intra-abdominal hypertension is usually defined as an IAP > 12 mm Hg or an APP < 60 mm Hg.

When IAP rises to a critical level it not only compromises blood flow to intra-abdominal organs, it also produces deleterious effects on the respiratory, cardiovascular, and central nervous systems. Various grading scales of intra-abdominal hypertension have been proposed such as the one shown in Table 165.1.

Abdominal compartment syndrome (ACS) may be defined as an abdominal pressure more than 25 mm Hg, APP less than 50 mm Hg, or with one or more organs showing signs of dysfunction at IAP > 20 mmHg [31a,b].

Clinical Manifestations

Increases in IAP impact virtually every system in the body. Often the first measurable findings involve the respiratory system where increased IAP is often the cause of increased $PaCO_2$ due to altered distribution of ventilation. This is usually followed by increased airway pressure and decreased pulmonary compliance, both static and dynamic [32,33]. These changes are often not correctly attributed to increased IAP because there are a multitude of other possible explanations such as pulmonary edema, acute lung injury, and so on.

Increased IAP increases renal vein pressure with elevations in plasma rennin and aldosterone as well as decreased renal blood flow, glomerular filtration, and urine output [34]. The fall in urine output may briefly be offset by volume expansion but as the pressure in the abdomen rises, this ceases to be effective and BUN and creatinine increase.

The increase in IAP results in an elevated CVP and pulmonary capillary wedge pressure as the volume is shifted into the thoracic cavity. In spite of this, actual venous return and cardiac output decrease and systemic and pulmonary vascular resistance increase. This compromise in venous return is transmitted to the CNS with resulting increase in intracranial pressure and decrease in cerebral perfusion pressure.

Management of Intra-abdominal Hypertension

In patients judged to be at high risk for the development of ACS, the risk may be reduced by leaving the abdomen open at the time of surgery. Similarly, a patient who is very difficult to close due to edematous bowel or pelvic hematoma may be better managed as an open abdomen from the beginning (Fig. 165.1). Anytime there is a suspicion of ACS, the initial diagnostic step should be the measurement of IAP, usually by the bladder. If IAP is elevated to harmful levels the only

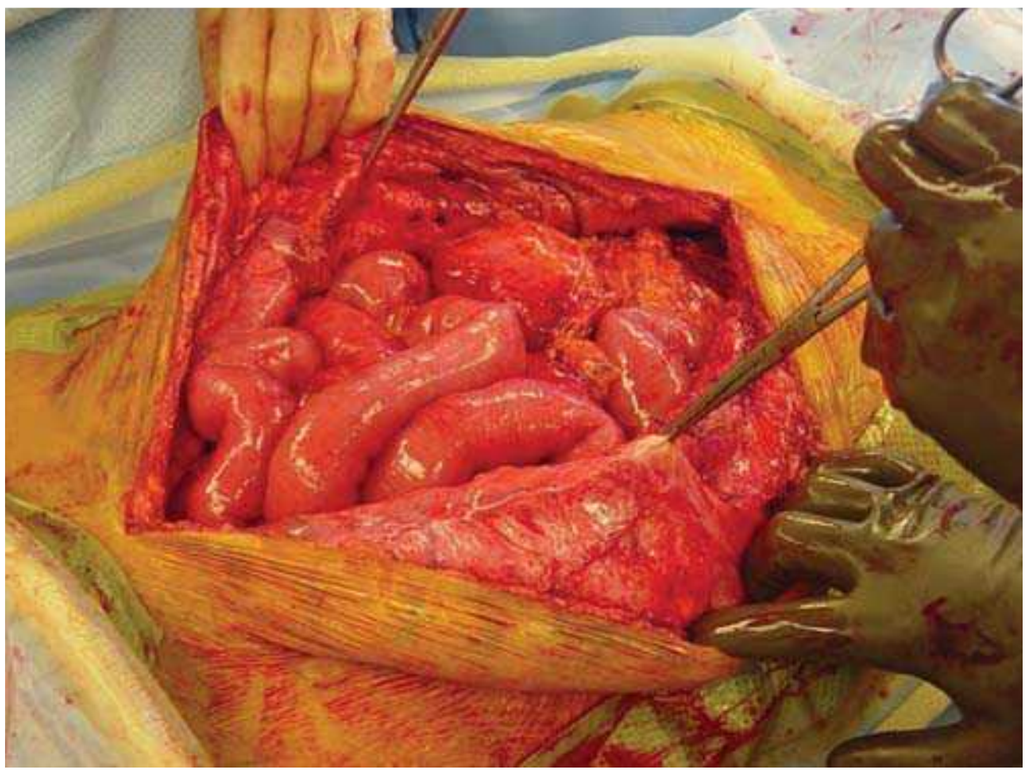

FIGURE 165.1. Massive bowel edema following damage control surgery for a gunshot wound to the abdomen preventing its closure.

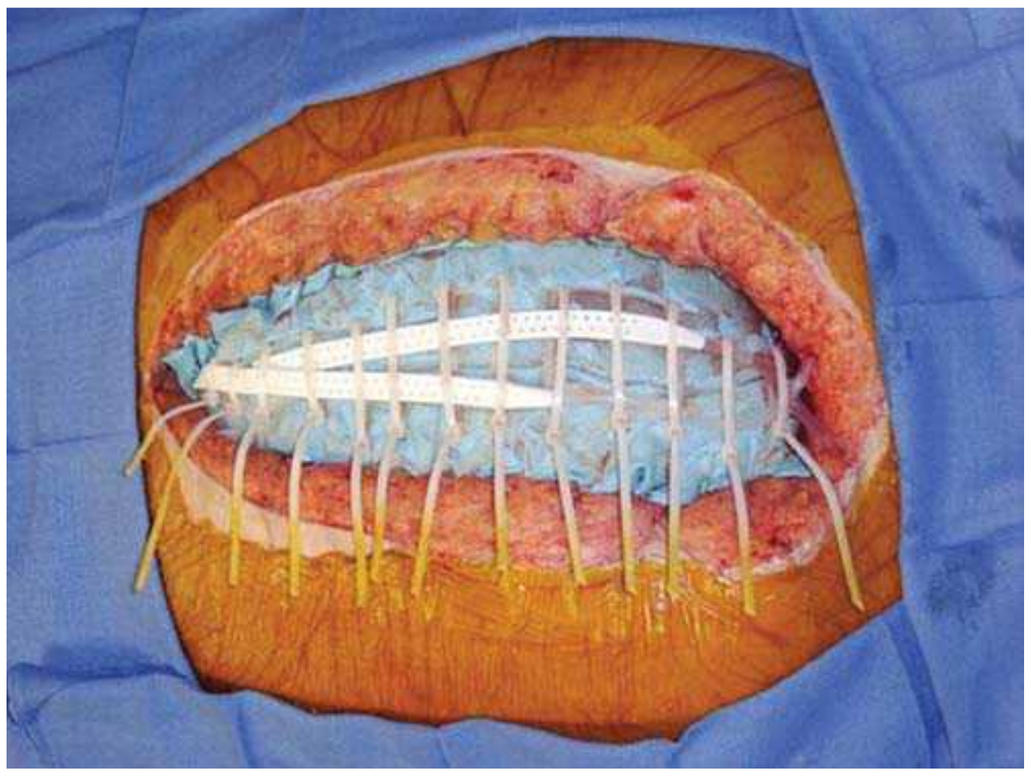

FIGURE 165.2. Homemade vacuum pack dressing for temporary closure of a damage control abdomen.

therapeutic choices are to either remove a portion of the contents or to enlarge the compartment. The next step is a determination of what is causing the increased pressure if this is not already known. Bedside ultrasound will allow the determination of whether there is a large quantity of free fluid in the abdomen. If so, either simple paracentesis or the insertion of a drain may resolve the problem. Large quantities of fluid within distended bowel loops may be reduced with a nasogastric tube. IAP may also be reduced in some patients with the use of improved analgesia and/or pharmacologic muscle relaxation. While these few special cases should not be overlooked, most cases of ACS will require surgical decompression and some form of temporary abdominal closure.

Open Abdomen

Patients whose abdomen is opened to prevent or treat ACS will require some alternative method of closure to prevent evisceration, to reduce fluid and heat loss, and to minimize loss of domain of the abdominal viscera. One of the easiest forms of closure that allows expansion of the abdominal cavity is the towel clip closure. This technique is based on the rapid closure of the skin only with multiple surgical towel clips [35]. The success of this technique depends on the elasticity of the skin to allow expansion of the visceral compartment. While it is simple and fast, towel clip closure has largely been abandoned in recent years as it has been recognized that a significant number of patients developed a recurrent compartment syndrome as the elastic limits of the skin were reached and exceeded. The gap in the *linea alba* has also been bridged with absorbable mesh or simple gauze packing [36]. Other popular techniques have been based on the silo idea similar to that used for newborns with gastroschisis [35]. Several materials have been utilized for the silo from 3 liter bags of fluid to adhesive drapes to sterile silastic sheets.

Currently the most popular management of the open abdomen is some form of vacuum pack dressing [37] (Fig. 165.2). The fundamental principal is the application of a nonadherent barrier over the bowel followed by some form of negative pressure connection and then a closed, sealed covering over the abdomen. The benefits of such a negative pressure dressing include the more rapid removal of fluid from the peritoneal cavity and the collapse of any free space in the abdomen. The negative pressure should also assist with the more rapid mobilization of edema from the bowel and abdominal walls and possibly minimize the contracture of the abdominal wall muscles. A number of homemade devices have been described and a commercial system is now also available.

When the bleeding has been controlled, the edema is resolving, and the packing has been removed, the next priority is abdominal closure. The longer the abdomen remains open, the greater will be the difficulty in achieving closure. Efforts to reduce the volume of the abdominal contents will include dieresis, removal of packing, and removal of fluid collections or hematoma. Actual re-approximation of the midline fascia may be facilitated by frequent "reefing" of the closure in a manner analogous to that employed in neonates with a silo, by the use of pharmacologic muscle relaxants or by more complex surgical techniques such as component separation [38]. In some patients, the bowel may heal into a solid mass prior to achieving closure. In these cases, a planned ventral hernia is the best option available with skin closure accomplished by either elevating skin flaps directly over bowel or by performing a split thickness skin graft directly onto bowel.

Prolonged exposure of the bowel by any of these techniques results in a substantial risk of enterocutaneous fistula formation. Fistula formation into such large open wounds almost never allows spontaneous fistula closure and greatly complicates the wound management as well as fluid and nutritional management. The primary goal of this phase of open abdominal management is to achieve some form of wound closure before fistula formation occurs.

DAMAGE CONTROL SURGERY

Historically trauma surgeons were taught that all bleeding must be stopped, all sources of contamination repaired or exteriorized, and other injuries definitively repaired prior to closing the abdomen regardless of the duration of the operation. However, with a better understanding and improved recognition of the metabolic failure that accompanies the so-called "bloody vicious cycle" of hypothermia, acidosis, and coagulopathy, current practice calls for a more abbreviated surgical technique referred to as damage control surgery [39]. These techniques should be employed only in the small percentage of patients with life threatening injuries complicated by profound shock. Damage control surgery as generally practiced consists of three phases:

I. Limited operative intervention to control hemorrhage, usually by ligation, shunting, or packing and to control contamination usually by ligation or stapling.

Little or no repair or reconstruction is performed at this stage. Closure is rapid and temporary.

II. Resuscitation to include aggressive correction of volume and hemoglobin deficits, replacement of coagulation factors, correction of acidosis, and restoration of body temperature usually carried out in the ICU.

III. Planned return to the operating room to complete definitive repairs, remove packs, and look for additional injuries. Definitive closure may be accomplished at this time or delayed for a later time. This phase should take place only when the deficits described above have been corrected.

Inability to correct the deficits described above may reflect continued bleeding. It is not difficult to overlook a surgical bleeding site when it is obscured by diffuse nonsurgical bleeding. Despite this fact, making the decision to return to the OR before correction of the deficits is a difficult one. Various criteria have been described for emergent return to the OR [40] but in practice the decision is often based on progress or the lack thereof. If the temperature, the pH, the coagulation studies, and the vital signs are getting better, it is usually worth persisting with the resuscitation efforts. If over a predefined time period of 2 to 3 hours of maximal effort most of these parameters are not improving, it is worth the risk of transporting the patient back to the OR for another look. Another indication for cutting short the resuscitation period is the development of an abdominal compartment syndrome that is limiting ventilation or cardiac output.

Acidosis

Hypovolemic shock in the severely injured patient produces a metabolic derangement that will not have disappeared with the restoration of normal vital signs. One manifestation of this metabolic failure is a persistent lactic acidosis. A variety of endpoints for resuscitation have been proposed including CVP, wedge pressure, oxygen delivery, oxygen consumption, and right ventricular volume but none have been shown to be more reliable than resolution of the lactic acidosis. Although crystalloid undoubtedly has a place in this resuscitation, recent data suggests that more of the resuscitation should be based on PRBCs, fresh frozen or thawed plasma, and platelets [41]. The traditional ratio has been one unit of plasma for each four units of PRBCs but current information suggests that a ratio closer to 1:1 may be advantageous. Spontaneous resolution of the acidosis with resuscitation suggests that the oxygen debt incurred during the shock phase is being repaid and serves as a marker of adequate resuscitation. However, during severe acidosis the patient is at increased risk for cardiac arrhythmias and becomes unresponsive to catecholamines either endogenous or exogenous. Coagulopathy is made worse by severe acidosis. Thus, it may be appropriate to use alkalinizing agents such as sodium bicarbonate or THAM (trishydroxymethylaminomethane) to raise the pH to approximately 7.2 [42]. Although the use of such agents is widely practiced, their use is largely based on *in vitro* data and theory. There is no clinical proof that they are beneficial. Evidence of supranormal oxygen delivery or consumption during resuscitation have been proposed as appropriate goals of resuscitation but current evidence suggests that they should be considered as predictors of improved outcome rather than therapeutic goals [43].

Hypothermia

If a patient's last body temperature prior to leaving the OR was less than 35°C, the risk of death is more than 40× greater than for patients with final body temperature more than 35°C. [44]. Hypothermia in the abdominal trauma patient is a multifactorial problem. Many patients arrive hypothermic due to exposure and shock prior to presentation to the trauma center. This problem is often compounded by further exposure to cold environments in the ED or the OR, the infusion of cold fluids, and the open body cavity. Inadequate oxygen delivery leads to inadequate oxygen consumption and a failure of heat production. This may be worsened by vasodilation from either intoxicants or anesthetic agents and loss of shivering ability from muscle relaxants. It is critical to prevent the development of hypothermia since it is very difficult to correct once present.

However, despite efforts in the ED and the OR, many damage control patients will be delivered to the ICU already hypothermic. In this circumstance, aggressive efforts must be employed including warming all fluids, raising the room temperature to uncomfortable levels, covering all body regions including the head, and the use of warming systems such as the Bair Hugger®. Lavage of the NG tube or chest tube with warm saline solution may also be utilized. In severe cases of hypothermia, it may be appropriate to utilize continuous arteriovenous rewarming as described by Gentilello et al. [45]. The inability to correct hypothermia if these measures have been employed usually indicates a failure of adequate resuscitation and that oxygen consumption is still inadequate.

Coagulopathy

The coagulation abnormalities associated with severe trauma include dilution of clotting factors and platelets from crystalloid infusion, consumption of clotting factors, hypothermia, and the anticoagulant effects of fibrin degradation products. In addition, there is the increasing use of anticoagulants and antiplatelet agents in patients with underlying comorbidities. Current data suggests that the coagulopathy of trauma and shock can be minimized by the use of blood component therapy with ratios closer to those of whole blood [41].

Upon arrival in the ICU from the initial phase of damage control surgery, blood should immediately be sent to the laboratory for clotting studies including prothrombin time, activated partial thromboplastin time, platelet count, and fibrinogen level. Hypothermia and acidosis impair the coagulation process and should be the initial focus of ICU care since factor replacement will have limited benefit in a patient who is hypothermic and acidotic.

Patients with prolonged clotting times should have aggressive replacement of clotting factors with fresh frozen or thawed plasma, while those with low levels of fibrinogen should also receive cryoprecipitate. Platelets should be replaced to achieve levels of more than 100,000 per μL.

Patients with nonsurgical bleeding who are judged to have adequate factor replacement and who are not extremely acidotic or hypothermic should be considered for the administration of recombinant Factor VIIa (rFVIIa). Although not formally approved for use in trauma patients, rFVIIa has shown benefit in two clinical trials of bleeding from trauma patients and while expensive, does appear to be safe in the injured patient [46].

SUMMARY

There are a host of similarities between the abdominal trauma patient and the general abdominal surgery patient and it has been assumed for the purposes of this chapter that the intensivist is familiar with managing these general surgical patients. This chapter has attempted to focus on the areas of abdominal trauma infrequently seen in general surgery or nonsurgical

patients. The elective abdominal surgery patient will usually have a single defined problem and will generally begin in a hemodynamically stable state. The abdominal trauma patient has an unknown number of injuries on presentation and the physiologic disruption resulting from the injury and the period of shock may compromise the ability to locate or repair all of them prior to arrival in the ICU. The trauma surgeon and the trauma intensivist must work in close cooperation since diagnosis, resuscitation, and treatment are a continuum beginning in the ED and extending seamlessly into the OR and the ICU. There should be no rigidly defined rules regarding who identifies the injuries or resuscitates the patient. Nowhere is the concept of the trauma team more important than in the ICU management of abdominal trauma patients.

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CHAPTER 166 ■ BURN MANAGEMENT

PHILIP FIDLER

DEFINITION AND GENERAL CONSIDERATIONS

A burn is a tissue injury resulting from excessive exposure to thermal, chemical, electrical, or radioactive agents [1]. The transfer of thermal energy over time is proportional to tissue damage.

In the United States, 60,000 to 80,000 people are hospitalized annually for burn care, but only 1,500 to 2,000 people sustain more than 40% total body surface area (TBSA) burns [2]. The elderly population is growing and contributes significantly to the increase in burn related hospitalizations. Among elderly victims, two thirds are flame burned, half have impaired judgment, and three fourths have a concomitant medical condition [2,3]. This population, typically debilitated by limited mobility, is particularly susceptible to large scald injuries, which can be devastating despite their clean appearance [4].

While all human tissue can be burned, the skin is most susceptible and is composed of essentially two distinct layers; the superficial epidermis, which is attached by a basement membrane to the foundation layer—dermis. The epidermis is of ectodermal origin and is invaluable for its vapor barrier, pigment, and immunological functions. While biologically very active, at approximately seven cell layers of keratinocytes, it has little mechanical integrity—the role of the dermis. Fortunately, the epidermis for practical purposes is "immortal" and when mechanically disrupted, will recover anew, without scar. In contrast, the dermis is derived from mesenchymal cells and provides the mechanical integrity to the skin, our "leather" so to speak, and has no native regenerative qualities. Dermis, when injured, repairs by way of scarring. Therefore, the essence of acute burn wound care is to sustain dermal viability.

The term burn will mean "burned skin of partial or full thickness depth." It is essential to discern between partial thickness and full thickness injuries of the dermis (commonly called second and third degree burns), as the latter requires operative interventions [2,3]. Pale, leathery, and insensate skin are features of full thickness injury, while blistering, weeping, pink and painful burns characterize partial thickness injury. Currently, no technology supersedes clinical experience in making this distinction, however, laser Doppler imaging has been validated in some centers [5]. Furthermore, the injury is dynamic and partial thickness injuries can worsen ("convert") to full thickness injuries for a variety of reasons.

When the burn injury coincides with blunt trauma, an evaluation for internal hemorrhage, closed head trauma, and long bone fractures is mandatory; the burned skin becomes a secondary concern [6]. Victim extrication from a closed space fire, such as in a bedroom, should make one expect an inhalational injury (see "Inhalation Injury"). The TBSA involved as partial and full thickness skin injury, age, comorbidities, and inhalational injury contributes to the morbidity and mortality of burn victims. Burns involving over 20% TBSA and those with inhalational injury of any burn size are at risk for burn shock (see "Burn Shock" section).

By the 1980s, a paradigm shift toward "early" (within 5 days) operative excision occurred because of the realization that the presence of burned tissue drives "burn shock" [6,7]. During the first half of the twentieth century burn wounds were treated with topical antibiotics and allowed to suppurate from the viable margin; subsequently, bacterial infections causing burn wound sepsis were commonplace [3,7]. The diminution of burn wound sepsis and advances in critical care borrowed from all disciplines have contributed to a remarkable LD50 for 90% TBSA burned in young people and 40% TBSA burned in the elderly [3,8] (Pruitt diagram; Fig. 166.1). Three clinical data points: age more than 60 years, TBSA burned more than 40%, and inhalational injury confer mortality rates over 90% when all three are present and 33% when two factors are present [8]. A rule of thumb with larger burns is a day in the ICU for each percentage of TBSA burned. Mortality usually occurs from multisystem organ failure secondary to sepsis. The substantial reduction in mortality at major burn centers has prompted research focus on improvement in quality of life [7]. Early transfer of patients to regional burn centers as per the guidelines of the American Burn Association has been shown to confer best outcomes [2,9].

BURN SHOCK

Burn shock is a form of vasodilatory shock, akin to "systemic inflammatory response," and creates an astounding volume requirement for the burned patient. It occurs most commonly with burns of at least 20% TBSA and is essentially universal in larger surface area burns. Increased vascular permeability and decreased capillary oncotic pressure combine to create severe edema, even in non-burned tissues. Kinins, serotonin, histamine, prostaglandins, and oxygen radicals are some of the vasoactive mediators released in response to burn injury and stimulate vascular permeability. Albumin is functionally lost into the interstitium thereby increasing extravascular oncotic pressure compounding the edema [3,10]. Unresuscitated patients perish from hypovolemic shock, historically likened to the demise from cholera; this association contributed to the understanding of the profound dehydration following burn injury [11].

While the resuscitation in burn shock may be conceptualized as optimizing the viability of the partial thickness (second degree) component of the burn injury, treatment is focused on intravascular volume repletion. Central shunting of blood compensates for the anhydremia, yet deprives the injured tissue of perfusion. Under perfusion deprives the partial thickness injury of essential nutrient delivery and gas exchange resulting in conversion of partial thickness injury to full thickness injury—which requires operative repair. Excessive resuscitation compounds tissue edema resulting in the same demise. It seems evolutionary biology has not accounted for intravenous fluid resuscitation, hence the response is maladaptive [12].

The patient's TBSA burn and weight dictates their fluid requirements for the first 24 hours. A number of methods to calculate the TBSA burned exist. The "rule of nines" and the Lund-Browder scales are useful for contiguous injury, while the palmer surface of the patient's hand, representing 1% TBSA, is used as a guide in noncontiguous injuries [3] (Fig. 166.2).

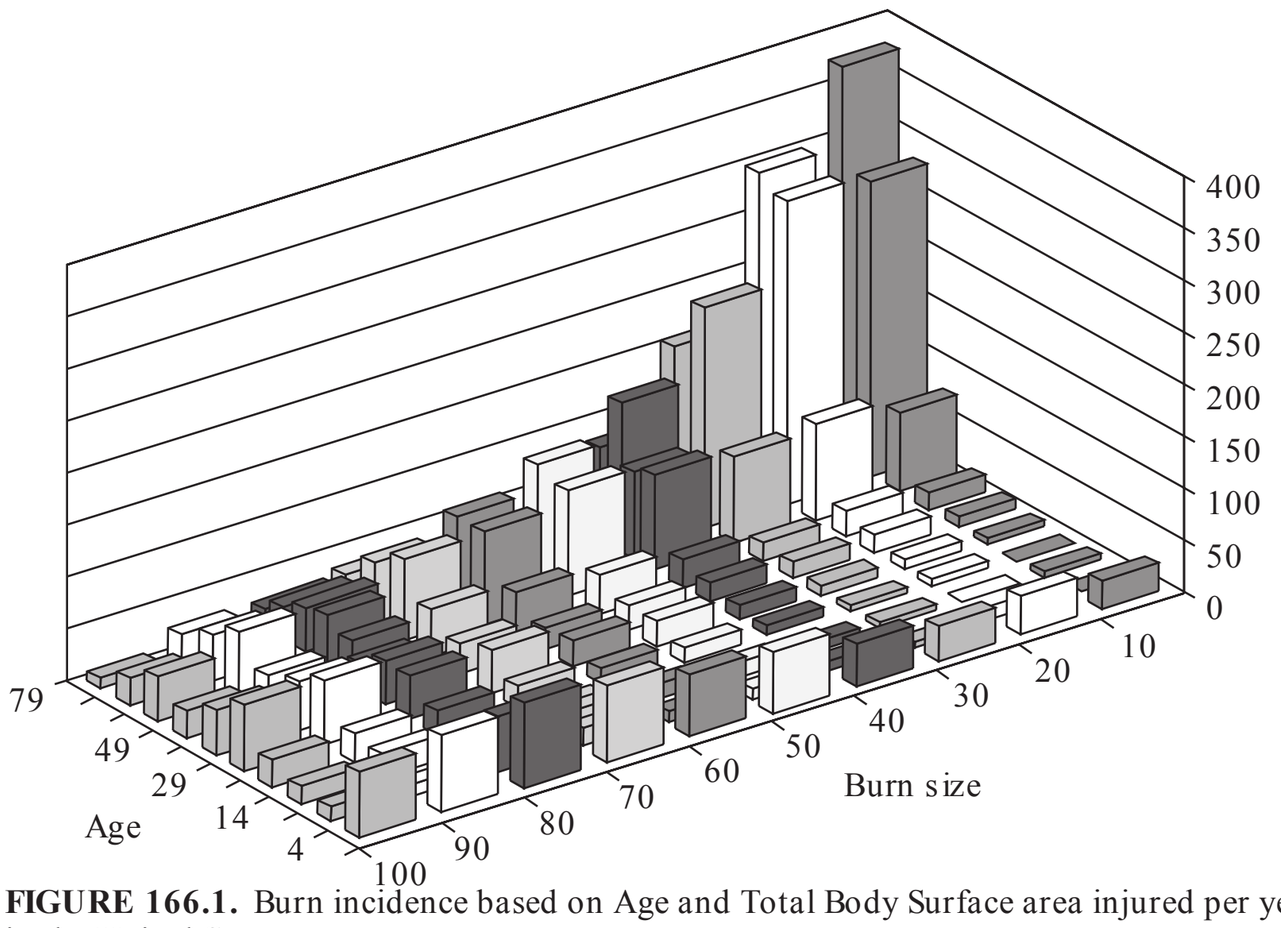

FIGURE 166.1. Burn incidence based on Age and Total Body Surface area injured per year in the United States.

Fluid "requirement" should be thought of as that volume needed to optimize organ function; debate continues over appropriate endpoints of resuscitation—most clinicians accept $^1/_2$ cc per kg per hour of urine output. If the urine output is more than 1 mL per kg per hour, then the rate of infusion should be decreased, this typically occurs by the third post burn day with the return of vascular integrity (See Fig. 166.4 Parkand formula). Thereafter, it is sufficient to limit the infusion and allow the concurrent insensible losses to correct volume overload—judicious diuresis with a loop diuretic may be employed. The timing and use of pressors requires clinical judgment in the face of hypotension despite adequate intravascular volume repletion. In patients with persistent oliguria, preexisting renal failure, or congestive heart failure, a pulmonary artery catheter is advised. While oliguria bodes poorly, excessive urine output should not be admired. If urine output is exceeding expectations, it is good practice to check the urine electrolytes, particularly for glycosuria and treat hyperglycemia accordingly [13]. Tight glucose control between 80 to 120 mg per dL with insulin is advocated [13].

The biological basis of burn wound conversion has not been fully elucidated. It is known that necrosis occurring from direct cellular damage and ischemia is not the only pathway. With cell death in evidence, the presence of apoptotic populations has been identified [14]. Macrophage inducible nitric oxide synthase may be an inciting factor in such apoptosis and its inhibition seems to limit apoptosis in animal models [14,15].

Central venous access is generally necessary because extremity edema makes peripheral access tenuous and is ideally, but not essentially, placed through non-burned tissue.

A number of resuscitative regimens have been advocated, none proven superior to date. Most are iterations of an isotonic solution in the first 12 hours of shock [3,11,15,16].

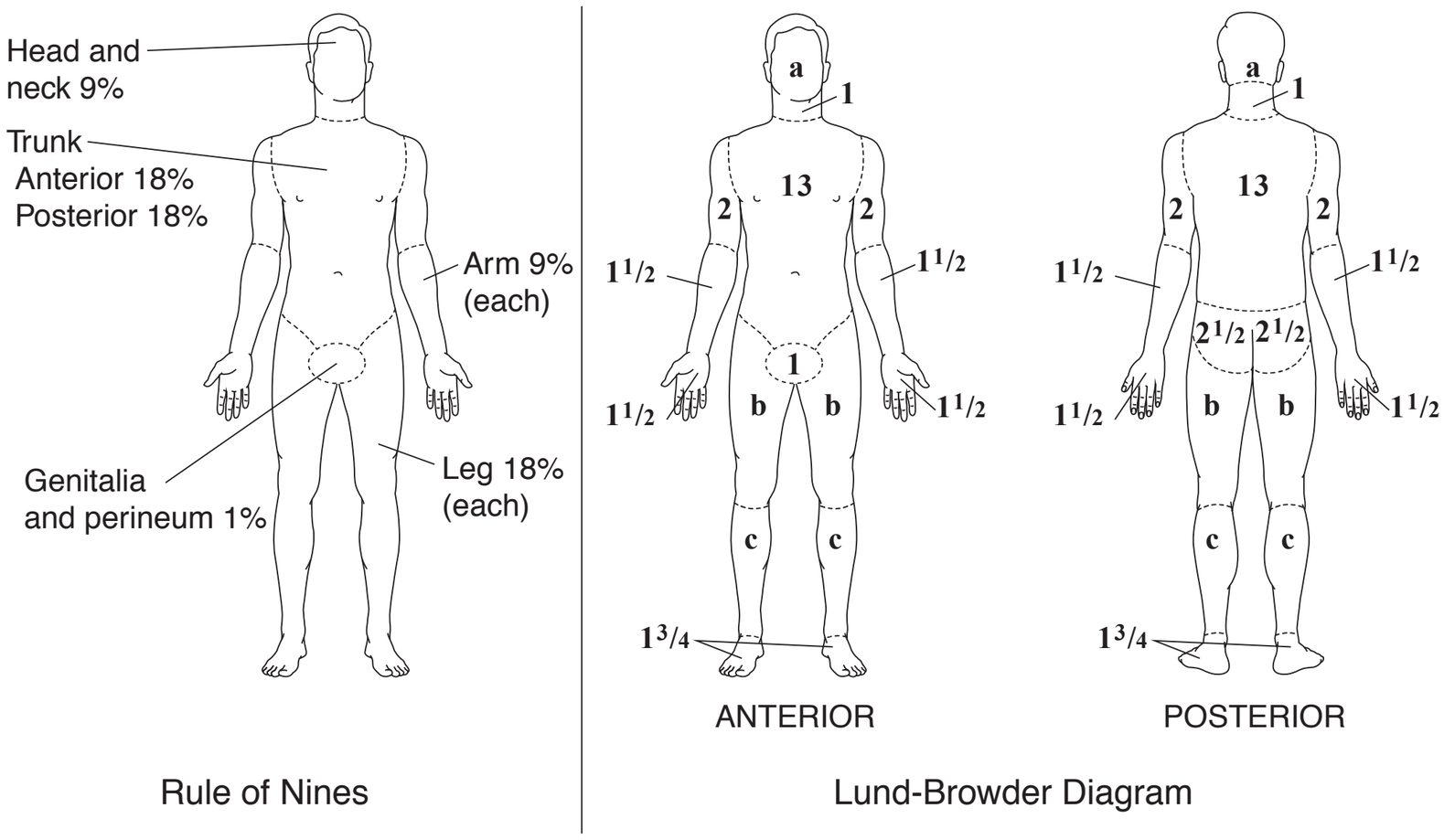

FIGURE 166.2. The Rule of Nines has been the primary method used to identify the percent of body surface burn. The Lund-Browder Diagram is a newer way of estimating the percent of body burn.

The use of colloid seems ill advisable in the first 12 hours after injury, as it seems to aggravate water loss into the pulmonary interstitium and potentiates pulmonary edema [3,15,16]. The commonest colloids are albumin, the most popular, and fresh frozen plasma (FFP). Proponents of albumin value its high oncotic pressure and maintenance of intravascular volume. Those against, argue that albumin is lost into the interstitium worsening edema there, possibly aggravating pulmonary edema. Again, the evidence suggests this risk is most pronounced within the first 12 hours post injury. Albumin is generally not used in patients with serum concentrations above 2.5 mg per dL. While FFP has less oncotic potential than albumin it may have a favorable immunomodulatory benefit, resulting in a truncation of the capillary leak associated with burn shock [3]. Both groups state that the use of colloid reduces the total volume of resuscitation and consequently protects against the detriments of excessive water administration. No level I evidence exists for the resuscitative fluid of choice [10]. A prospective, multicenter trial is needed to answer this question [10].

The pathophysiological similarities between septic shock, systemic inflammatory response, and burn shock may have a common pathway that could be interrupted to improve outcomes [17]. Beta blockade, antihistamines, FFP, generous narcosis, nonsteroidal anti-inflammatory agents, glucocorticosteroids and recently, drotrecogin alfa are amongst the many approaches investigated to mitigate this cellular "hysteria" [2,17]. None of these approaches have proven superiority in multicenter prospective trials to date.

The GI tract is an underutilized resuscitative venue and enteral hydration seems to have been forgotten with the advent of improved intravenous therapy [18]. Enteral nutrition and resuscitation may begin on the day of injury with the caution that patients in shock, requiring vasopressors, can develop bowel ischemia and enteral feeds may increase the metabolic needs of the gut, contributing to bowel ischemia and necrosis. Patient's not tolerating enteral feeds or those with abdominal hypertension (see "Abdominal Compartment Syndrome" section) should be given TPN; this is uncommonly necessary.

Adrenal insufficiency should be suspected when volume repleted hypotension persists despite pressors and is further suggested by concurrent hyponatremia and hyperkalemia. While the characterization of adrenal insufficiency is more expansive in the septic shock literature, numerous case reports and some prospective data support its presence in thermally injured patients. A high mortality exists when disturbances in the hypothalamic-pituitary-adrenal axis are found early in a patient's burn shock course [19,20]. One need not await the results of a corticotropin stimulation test in the face of circulatory collapse and glucocorticoid supplementation should be initiated. In questionable cases, a corticotropin stimulation test is confirmatory and not skewed by Decadron, which enhances vascular tone but has no mineral corticoid activity unlike hydrocortisone. A single blood cortisol of less than 15 μg/dL, in a stressed patient, is suggestive of insufficiency, and it is probably wise to supplement. Glucocorticoids are known to unfavorably affect skin engraftment, and this risk must be weighed against the patients' circulatory failure. Vitamin A supplementation seems to limit the unfavorable wound healing delays and atrophy seen with glucocorticosteroid therapy [20,21].

INHALATION INJURY

Burn victims have two unique pulmonary disorders: restrictive respiratory failure secondary to burn eschar involving the anterior torso and inhalational injury. Torso eschar needs to be divided (see "Escharotomy" section).

An inhalational injury occurs when toxic combustants have been inhaled, and cause a severe inflammatory response in the bronchial pulmonary tree and systemically [22,23]. Extrication from a smoke filled room and findings of singed facial structures, carbonaceous sputum, and respiratory distress corroborate the diagnosis but are not exclusionary. Approximately 30% of adult burn admissions have inhalational injury, which increases mortality rate for like burn size [8,9]. Concurrent inhalational injury intensifies burn shock and may require up to 50% more fluid for adequate resuscitation [3,24,25]. This component of the inhalational injury cascade seems driven mainly by the sensory neuronal pathway, as it can be truncated by capsaicin blockade in an experimental ovine model. Histamine, cyclooxygenase, and atropine blockade do not decrease the response [23,26,27]. Neutrophils invade alveolar spaces via the pulmonary vasculature and likely contribute to O_2 radical production and injury [27,28].

Airway management is paramount. One needs to be particularly observant for signs of upper airway obstruction, secondary to edema, which often develops hours after initial injury. Stridorous patients should be intubated urgently; preferably with an 8 fr endotracheal tube to allow for bronchoscopy and toilet. Immediate threats to life are, in particular, carbon monoxide (CO) poisoning and cyanide (CN^-) toxicity. Generally the lethal level is >60% COHgb and 100% mask O_2 should bring the half-life of COHgb to normal within an hour's time [29]. CN^- poisoning causes cytochrome oxidase inhibition and loss of hypoxic pulmonary vasoconstriction increasing dead space. CN^- is lethal in levels over 1 μg per mL, while 0.02 μg per mL occurs in healthy nonsmokers [25,29]. It would seem rare to have an increased CN^- level without corresponding increase in COHgb; thus, it is fair to say that a normal COHgb, for practical purposes, rules out CN^- toxicity [22,29].

Inhalational injury may best be thought of as a syndrome with a number of sequelae, including endobronchial and interstitial edema, alveolar damage, mucociliary dysfunction, endobronchial slough with cast formation, functional pulmonary shunting, and decreased compliance. Increased bronchial blood flow causes increased interstitial edema [23]. In time, the bronchial epithelium sloughs and combines with exudates and fibrin to form aggregates ("plugs") that support bacterial growth. The tenacious plugs create subsequent mechanical airway obstructions. While there is a dearth of prospective data, aerosolized heparin in conjunction with *N*-Acetyl-cysteine, is advocated in some centers to prevent cast formation and seems particularly helpful in the pediatric population where the narrower airways are at greater risk for obstruction [30]. Burn victims are susceptible to pneumonia because of their immunocompromised state, their immobility, and inability to clear secretions.

Ongoing study of the mechanisms of this form of shock and pharmacological interventions are being intensely investigated. Currently, no objective scale of severity for inhalational injury exists. Bronchoscopy is most useful to characterize the presence or absence of tracheobronchial inflammation and provide toilet.

Prophylactic antibiotics are not recommended. Pneumonia and tracheobronchitis should be treated by culture directed therapy, utilizing Gram's stain, culture of sputum, or bronchoscopy specimens, and local biograms [30,31]. Goals to minimize incidence revolve around proper toilet, limiting aspiration, utilizing lung protective ventilator management, and frequent surveillance [3,30,31]. Patients' overall condition and pulmonary performance by way of usual weaning parameters dictate extubation time. The risk of upper airway obstruction prior to extubation should be assessed by deflating the balloon and audible appreciation of air leak, "no air leak, no extubation." Laryngoscopy may reveal glottic swelling. Glucocorticoid steroids may be considered for the treatment of upper airway edema in lieu of an early extubation but are not

indicated for the pulmonary component of inhalational injury and not recommended when a large surface area burn is present. Healing time for patients with lower respiratory injury is longer [23]. The timing of tracheostomy has not been standardized but is probably beneficial in patients expected to be intubated beyond 3 weeks particularly for the benefits of oral hygiene, positioning, and earlier weaning.

SURGICAL CONSIDERATIONS FOR THE ICU

The decision to operate or manage partial thickness injuries expectantly is complex and depends on the location of injuries, patient condition, and survivability (see introduction).

Escharotomy

Full thickness burned skin (eschar) is a restrictive entity; its noncompliance, especially when circumferential, in the face of growing interstitial pressure deprives limb perfusion. This mandates operative release termed escharotomy, which is often limb saving. It may be performed at the bedside, ideally but not essentially, with electrocautery. Incisions are made through the eschar to relieve the underlying pressure. When eschar is involved around the chest wall, incisions are made along the bilateral anterior axillary lines craniocaudally and intercepted transversely joining these incisions at the approximate level of the second rib and xiphoid (Fig. 166.3). This maneuver releases the chest wall, enhancing tidal volume and decreasing airway pressure. If involving the neck region, incisions are made to allow jugular venous drainage. Rarely, lateral canthotomies, which are incisions through the lateral orbital skin and tendon of the canthus, are needed to release ocular pressure in the instance of retrobulbar edema. Although vigilance is the rule, the areas in question are typically apparent within the first 12 hours of injury.

Burn Wound Sepsis

Burn victims develop multiple defects in their immune system that predispose them to an increased risk of infection. Primary treatment is surgical excision and tissue coverage with autograft, skin substitute, or topical antibiotics, alone or in combination. This immunocompromised state combined with loss of the skin barrier can lead to severe infections. Topical antimicrobials (e.g., silver sulfadiazine or mafenide acetate), as well as local wound care, help decrease the amount of burn wound infections [2,6,7]. However, they cannot eradicate burn wound sepsis. Mafenide acetate penetrates eschar and is most effective against Gram negative organisms. It is known to cause metabolic acidosis as a carbonic anhydrase inhibitor and may select for fungal overgrowth.

The signs of burn wound sepsis are diffuse, typically a greenish grey discoloration of the burn, purulent fluid from the wound, and eschar separation along with cellulitis in the surrounding unburned skin. If not treated at the earliest possible time, systemic sepsis will develop. Diagnosis can be confirmed by biopsy of the wound but should not preclude total and urgent excision. Systemic antibiotics are started if infection is suspected and altered or stopped once burn biopsies for quantitative bacterial counts and blood culture results are obtained and negative for infection.

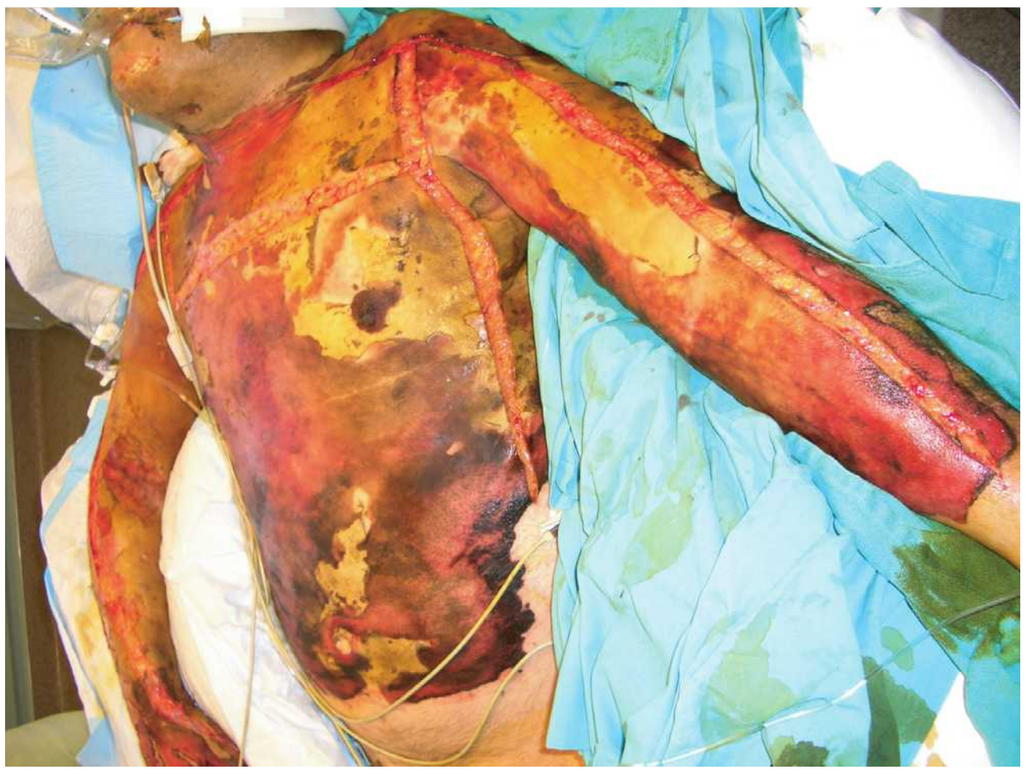

FIGURE 166.3. Burn patient with full thickness constricting torso burns. Escharotomy incisions are in progress to permit ventilation. A transverse abdominal or chevron subcostal incision (not shown) would complete the release.

Abdominal Compartment Syndrome

By transducing a transurethral catheter, the urinary bladder pressure is obtained as an indirect measure of intra-abdominal pressure. A measurement more than 20 cm H_2O is loosely defined as abdominal hypertension, which may develop into organ dysfunction, namely renal failure, respiratory embarrassment, and bowel ischemia and denotes abdominal compartment syndrome. Extrinsic renal vein compression leads to progressive oliguria, and respiratory failure is secondary to restrictive airway dynamics. The definitive treatment is celiotomy, although lesser interventions such as peritoneal drainage and or continuous venovenous hemodialysis (CVVHD) are under investigation [32,33].

Cardiovascular Response

Unresuscitated burn victims die of hypovolemic shock. An untreated victim would show progressively decreasing preload and cardiac output. Unfortunately, during the initial 12 to 36 hour postinjury period, even "adequate" volume repletion will not maintain cardiac output. Decreased cardiac contractility and diastolic dysfunction prevail. Animal data suggests a pro inflammatory mediated mechanism *vis-a-vis* the CD-14 and Toll-like–receptor 4 complexes–as seen with endotoxic shock; it is corroborated by echocardiographic abnormalities in burn victims [34,35]. This decrease in contractility is more pronounced in those with inhalational injury and is, in part, nitric oxide mediated [36]. This temporary, seemingly maladaptive cardiac dysfunction passes with time and is followed by a hyperdynamic cardiac performance, which is maintained, often for weeks, post burn [34].

Naturally, the elderly, particularly those with pre-injury cardiac compromise, are more susceptible to congestive heart failure. The quest to rule out an acute myocardial ischemic event will often reveal elevations in cardiac enzymes, both CPK and Troponin-I. Heart muscle is obviously compromised in burn shock, and serum levels of cardiac enzymes are often found within the range attributed to myocardial infarction in the "acute chest pain" setting [35,37]. This quandary is common—what to do about it? Surprisingly, the actual occurrence of a coronary artery thrombosis has rarely been reported. Cardiac stress or "Troponin leak" is seen in many shock states. Emergent cardiac catheterization based on these enzyme elevations

may be more harmful than helpful in that traveling long distances throughout a hospital with a critically ill burn victim has substantial inherent risks [38]. A 12-lead EKG should be obtained, and if regional ischemic pattern is present or is suggestive of coronary artery thrombosis or spasm, then a cardiac catheterization is prudent [35]. The lab value of Troponin-I or CPK-MB alone in the course of early burn shock should not dictate emergent catheterization.

Metabolic and Nutritional Considerations

The insensible fluid and protein losses from burn wounds are extraordinary. We know that protein catabolism, compounded by losses through the wound bed and the interstitium, results in severe hypoproteinemia. The hypermetabolic response that occurs, after a thermal injury is more than that observed after any form of trauma or sepsis [3,8]. The magnitude of the response parallels the severity of the burn to a maximum at a burn size of 60%. An increase in temperature of 2°F to 3°F occurs with this response. Patients are kept in a warm environment to help decrease the total energy expenditure [39]. The loss of vasomotor tone autoregulation, possibly in an effort to provide maximal nutrient delivery and gas exchange to the wounded tissues, results in significant evaporative heat loss. Hypothermia from weeping wounds and dwindling energy supplies from the catabolic, muscle wasting condition of burn shock is easily avoided with external warming. Burn centers often keep patients' rooms 90°F to 100°F in the hopes of shunting caloric needs away from thermostasis toward needed wounded repair [40].

Early surgical excision of the burn wound is the most effective means to this end; it truncates the shock state. Clearly, the presence of burned tissue drives the inflammation in the early post injury period, not to be confused with supervening bacterial sepsis, which often occurs days later or in neglected burn wounds.

Muscle wasting, a seemingly unavoidable complication of the hypermetabolism associated with burn wounds, can be ameliorated through anabolic enhancement [41,42]. The two most common approaches are recombinant Human Growth Hormone (HGH) and Oxandrolone. HGH is associated with hyperglycemia, often requiring insulin support and has largely been supplanted by Oxandrolone, which must be given enterally at 10 mg b.i.d., and so the effect is limited in the face of ileus [42,43]. A major thermal injury is characterized by increased muscle proteolysis, lipolysis, and gluconeogenesis. Burn wounds use glucose in greatly increased quantities. Hyperglycemia is common in burn catabolism and may exacerbate muscle wasting. Nonetheless, the known benefits of glucose control from other disease entities in the critically ill are likely to be beneficial in burn victims, and insulin supplementation is recommended [44]. Severe loss of nitrogen, which also occurs, needs to be replaced to combat the muscle wasting and to enhance the immune system. This replacement is absolutely necessary to fight infection and for wound healing. Burn patients need two to three times the basal energy expenditure. Significant burn injuries require 2 g per kg protein. Glucose should contribute 50% to 60% of the calories and the calorie-to-nitrogen ratio should approach 100:1 [43]. All attempts should be made to feed the patient enterally, as enteral feeding decreases the risk of infection. Nutrition may be started on the day of injury.

Infection and Immunity

Patients with significant burns are at high risk for infection, and this is often the precipitating cause of late deaths. The pulmonary tree and the wound beds themselves are the commonest sites and foci for fatal infection. Burn wounds, particularly devitalized full thickness eschar, provide fertile ground for bacterial growth. Early wound infections, within the first 10 days, are typically Gram positive organisms. Later, Pseudomonas is a common and potentially lethal organism, and even later, fungal infections may occur and portend an ominous sign [45]. When surgical excision is not an option, topical antibiotics are the mainstay. Other sites of infection include central lines and Foley catheters. A strong belief exists that the intestine may be a source of unexplained bacteremia by bacterial translocation. This risk may be decreased by enteral feedings. Immunoenhancing regimens are an area of intense study [43,46]. The integrity of the atrophied GI tract is compromised, leading to translocation of bacteria, toxins, or both, putting the burn victim at risk. Evidence demonstrating the presence of bacteria and endotoxin in the lymphatic system makes a plausible case for concern.

ELECTRICAL INJURY

Electrical injuries are divided into high voltage (more than 1,000 volts) or low-voltage injuries (less than 1,000 volts). Low-voltage injuries present as thermal burns, with injuries to the tissue from the outside in. High-voltage injuries may present with little injury to the skin, but significant injuries to the muscle, vasculature, and the bone underneath [47]. Very high voltage injuries occur with obvious disruption of the soft tissue common in electrical line workers. Electrical injuries vary with the source voltage, contact time, and current pathway [2,47,48].

Immediate threats to life are dysrhythmias and spinal cord injury, from either direct nerve injury or tetany resulting in spinal column fracture and cord injury [49,50]. The latter can cause mechanical respiratory failure and paralysis [47,48]. The cutaneous lesions may be subtle and efforts should be made to find entrance and exit lesions, as these will direct the practitioner to focus on the intervening tissues. Compartment syndromes from myonecrosis are common, particularly in the upper extremities, and compartment releases by fasciotomy should be pursued. Often nonviable muscle needs resection. Fluid resuscitation must be initiated quickly; frequently, these patients require a higher volume of fluid due to the underlying tissue injury. Myonecrosis will lead to myoglobinuria, which can lead to renal failure. Serum levels of creatinine phosphokinase into the tens of thousands are often present, and the risk of renal failure is reduced by maintaining a high urine output of 100 mL per hour. Mannitol may be added once resuscitation is well underway. Alkalinizing the urine is advocated by some with the theoretical benefit of preventing heme pigment sedimentation; however, at present, it is by no means mandatory. Pyrophosphate scanning can be used to find occult myonecrosis [51]. One may find serial daily monitoring of the CPK helpful to assess the extent of muscle damage and recovery. Persistent elevations are suggestive of skeletal muscle necrosis and surgical debridement is likely to be beneficial [47].

CHEMICAL INJURY

Acids, "burn" by coagulation necrosis, creating an eschar that limits deeper penetration, whereas alkali, "burn" by liquefaction necrosis in the subcutaneous fat, creating vascular thrombosis and subsequent dermal ischemia. Hydrofluoric acid (HF) burns carry the unique concern of calcium and magnesium chelation and risk cardiac arrest secondary to severe hypocalcemia; intra-arterial infusion of calcium gluconate has been met with some success and may limit digital ischemia and

intravenous calcium repletion is necessary. A calcium gluconate slurry may be massaged into the exposed area to potentiate systemic absorption of HF.

PSYCHIATRIC AND ANALGESIC CONSIDERATIONS

Theoretically, those with altered thought processes or coping skills are accident prone. Suicide attempts by self-immolation account for as many as 5% of seriously burned adults. The concurrence of a serious psychiatric comorbid condition is alarmingly high in burn victims and is estimated between 30% and 70% [3].

Burns are commonly known to be one of the most painful medical conditions. No single analgesia regimen can possibly characterize the needs of all burn victims, and suffice to say, the uninitiated practitioner may find the dosing of narcotics multiples of what is commonly used post surgery. Generally, narcotics and benzodiazepines are given as continuous drips; it is common to have moderately burned patients on morphine drips of 10 to 20 mg per hour and benzodiazepines coinciding at 1 to 4 mg per hour. Overtime, the large doses require large volumes of distribution and tolerance lead to even higher dosing. Unlike other critically ill patients, it is not prudent to eliminate these medications for frequent "full" neurological assessment. The physiological benefit of "successful" doses of these medications goes far beyond simple mercy, but portends toward decreased catabolism, cardiovascular stress, and reduced risk of posttraumatic stress disorder [4]. Once the patient's burn wounds have been managed adequately, and wound closure and burn shock are resolving, a stepwise weaning of these agents is done to permit ventilator weaning and to avoid sequelae of withdrawal.

Parkland Formula: Total Fluids for 24 hours
Ringers Lactate = 4 cc × kg × % BSA
Example: A 70-kg man with a 50% TBSA burn would thus have a total deficit of 14 L (4 cc × 70 kg × 50% BSA = 14,000) in 24 h. Half the 24-h deficit should be repleted in the first 8 h, due to the high risk of hypovolemic shock early in the course. In this example that is 7 L within the first 8 h would mean a rate of 875 cc/h for the first 8 h. It is important to note that this recommendation starts at the time of injury, and often, patients are brought in hours after injury, often necessitating an increase or decrease in the rate to insure that this amount is given within the first 8 h. The rate would subsequently be decreased to **438 cc/h** for the next 16 h. The formulas are used to determine how much fluid should be given to the burn victim in the first 24 hours. Both formulas are being used today. The Brooke formula is the military formula and our service personnel will be resuscitated using this formula. Many of the other burn centers use the Parkland formula which was developed at the Parkland Trauma Center in Dallas, Texas.

FIGURE 166.4. Modified Brooke Formula:
Total Fluids for 24 hours
Ringers Lactate = 1.5 mL × kg × % BSA
Plasma = 0.5 mL × kg × % BSA
D5W = 2,000 mL

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CHAPTER 167 ■ ORTHOPEDIC INJURY

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EPIDEMIOLOGY

Blunt and penetrating trauma kills more than 100,000 people in the United States each year, is the leading cause of death in Americans younger than 45 years of age, and results in staggering losses of health in surviving trauma patients, with associated losses of economic productivity [1]. Trauma evacuation systems have improved dramatically over the past few decades, and patients are much more likely to survive injuries that would have resulted in early mortality only 30 to 40 years ago. Many polytraumatized patients sustain orthopedic injuries, such as extremity fractures, pelvic fractures, or dislocations. These need to be recognized and addressed appropriately to minimize consequent morbidity and mortality. A dedicated orthopedic trauma service, specifically constructed to manage patients with complex fractures and dislocations in the setting of other systemic injuries, may be associated with improved outcomes for trauma patients. The orthopedic traumatologist is not only trained in the surgical management of the individual orthopedic injuries, but is also comfortable with functioning as a member of a multidisciplinary team that, of necessity, also includes emergency physicians, abdominal and chest surgeons, neurosurgeons, urologists, and plastic surgeons, to name a few.

Musculoskeletal injuries in trauma patients come in many varieties. Articular (joint) fractures represent complex injuries requiring prolonged reconstruction; although they routinely occur in polytraumatized patients, their management is beyond the scope of this discussion. Long bone (femur, tibia, humerus, forearm) fractures can have direct impact upon a patient's early mortality and late morbidity. Pelvic fractures are associated with early mortality, and their recognition and acute management is vital as part of the life-saving efforts of the trauma team. Open fractures are associated with the development of sepsis if not properly addressed. Compartment syndrome, a sequela of severe extremity trauma, is a soft-tissue condition that can result in early morbidity, associated with the impact of myonecrosis on renal function, as well as late disability, associated with fibrosis of one or more muscles important for activities of daily living. Venous thromboembolic (VTE) disease is a danger for all trauma patients, and the risk of VTE has been shown to be increased significantly in patients with pelvic and hip fractures. Finally, lesser fractures can have dramatic implications on future function for trauma patients; it has been shown that failure to identify and/or address complex injuries of the foot, for example, is associated with poor long-term outcomes in patients who survive major trauma [2,3].

In this chapter, we will introduce challenges and knowledge associated with multiple problems that affect trauma patients: open fractures, pelvic fractures, long bone fractures, knee dislocations, compartment syndrome, deep venous thrombosis, and neurological injury. It is our goal to discuss orthopedic treatment considerations for all of these trauma sequelae such that they can be integrated into the management of the patient who is the victim of multiple trauma.

OPEN FRACTURES

Open fractures, or fractures with associated skin wounds allowing communication of the external environment with the fractured bone surfaces, are present in a high percentage of polytraumatized patients. Frequently, the open fracture wound contains gross contamination, including dirt or vegetable matter, clothing, or glass. These wounds historically are at high risk of infection without adequate and early treatment of the open wound. Management protocols for open fractures are different from those for closed fractures, and considerations regarding timing of definitive stabilization of both types of fractures may differ. The basic treatment protocol for open fractures includes

antibiotic administration, wound debridement, wound irrigation, fracture stabilization, and wound closure or coverage.

The Gustilo-Anderson classification scheme is the most widely utilized classification for open fractures. It was initially published in 1976 [4]. Type I open fractures are fractures with a clean wound measuring less than 1 cm in length. Type II open fractures are fractures with a laceration measuring more than 1 cm in length and without extensive soft tissue damage. Type III open fractures are fractures with extensive soft tissue damage or an open segmental fracture (a two-level fracture of the same long bone). "Special categories" were created for open fractures associated with vascular injuries, farm injuries, and high-velocity gunshot wounds. Type III fractures, therefore, represented a highly heterogeneous group of severe open fractures; a modification of the classification scheme for type III open fractures, published in 1981, was therefore developed [5]. Type IIIA open fractures have extensive soft tissue damage but adequate soft tissue coverage, or are the result of high-energy trauma irrespective of laceration size. Type IIIB open fractures entail extensive soft tissue loss, periosteal stripping, bone exposure, and massive contamination. No mention of requirement for muscle flap fracture coverage is made by the authors (despite the fact that many of these wounds indeed do require flap coverage); this is a bastardization of the classification that has been propagated over the years [6], although it was suggested by Gustilo himself in a subsequent letter to the editors of the *Journal of Bone and Joint Surgery* [7]. Type IIIC open fractures are those associated with a vascular injury that (importantly) requires repair; those open fractures associated with arterial injuries that are not repaired do not fall into this type. An important point must be made about this classification scheme: it is best utilized during operative debridement of the open fracture. The presence of a small open wound in the skin may belie the extensive soft tissue injury underneath, leading to a misclassification of the open fracture. However, this may be of relative unimportance, as the reliability of this classification scheme has been questioned [8–10].

Antibiotic administration has been shown to be highly effective in decreasing infection rates after open fractures [11]. Short courses of first generation cephalosporins (typically, cefazolin), initiated as soon as possible after injury, appear to be beneficial in limiting infections after open fracture [12]. Aminoglycosides and penicillins are often utilized in the treatment of type III open fractures and highly contaminated open fractures [13], respectively. Older studies have demonstrated that administration of broad-spectrum antibiotics lead to decreased infection rates [14]. However, the scientific evidence for this practice is limited [12]. Administration of aminoglycosides for the treatment of open fractures must be accomplished judiciously to minimize risk of oto- and nephrotoxicity. Quinolone antibiotics, effective against gram-negative bacteria, have been shown to be effective at reducing infection rates for type I and type II open fractures [15], but they may have an adverse effect on fracture healing; this effect has been shown in animal studies [16,17]. Duration of antibiotic administration is a matter of debate. Older recommendations included 72 hours of antibiotic treatment for types I and II open fractures and 120 hours for type III open fractures [18]. However, Dellinger et al. published in 1988 that a single day of antibiotics is as effective as 5-day regimens for preventing infection after open fracture, in a prospective randomized trial [19].

Surgical debridement of open fracture wounds in a complete and expeditious manner is likely the most important factor in successful management. Sharp debridement should be meticulous and methodical. All foreign material is removed. Bone ends should be delivered into the wound, and complete exploration of the injury zone is necessary. Often, long longitudinal extensions of the traumatic wound are necessary for adequate exploration. All tissue which is completely devitalized, including bone fragments devoid of soft tissue attachments, should be removed [20,21]. Judgments related to the removal of large articular (i.e., joint surface) fragments may be required to balance the risk of severe disability with loss of said fragments *versus* risk of infection with their retention. Devitalized extra-articular fragments can be cleaned and used as a reduction aid intraoperatively if fixation is proceeding immediately, or they may be stored and utilized later if fixation is delayed; these fragments are ultimately discarded [22]. In general, therefore, it is better not to discard bone fragments from open fractures until the patient has arrived in the operating room for definitive management of the open fracture by the orthopedic surgeon.

Wound irrigation generally follows sharp debridement. Little data exists on the type of irrigant, the amount of irrigant, and the method of irrigation that is the best. Irrigation solutions generally are based upon normal saline (0.9% NaCl). Additives historically have included bacitracin, cefazolin, neomycin, soaps, bleach, Betadine, and other antiseptics (such as benzalkonium chloride). Some of these, such as antiseptics, have been shown to be detrimental to wound viability [23]. Antibiotics appear to offer no benefit over normal saline alone [24]. A prospective, randomized study revealed that a nonsterile soap solution demonstrated decreased wound complications and equal efficacy at reducing infection after open fracture as compared to a sterile saline solution containing bacitracin [25]. A recent survey of nearly 1,000 orthopedic surgeons revealed a high preference for saline irrigant [26]. High *versus* low-pressure lavage for open fracture wounds has also been a source of debate. Although high-pressure lavage has been thought historically to be better for removal of surface bacteria and inorganic material from soft tissues, it is damaging to both soft tissues and bone, and there is some evidence that it can *increase* bacterial penetration of bone in an animal model [27]. The same survey of 984 orthopedic surgeons who revealed a preference for saline irrigant also revealed a preference for low-pressure lavage for open fracture wounds [26]. No consensus exists on the volume of irrigant. Protocols vary between institutions and even within institutions, based upon surgeon preference. Up to 9 liters of irrigant are utilized in some centers, but there is no scientific evidence upon which a recommendation can be based. Ultimately, it is the opinion of most surgeons that wound debridement is the most critical aspect of treating open fracture wounds, and that the irrigation component of this treatment is of relatively less importance.

Methods of fixation for open fractures are variable. Historically, acute open reduction and internal fixation of open fractures was contraindicated, without good scientific evidence. However, the Harborview group in Seattle demonstrated that acute open reduction and internal fixation of open ankle fractures is a safe and effective method of treatment [28]. External fixation is relatively rapid and fixation points can be kept out of the zone of injury. Mobilization of fracture ends can be accomplished at the time of future debridement, if necessary, and staged open reduction and internal fixation with external fixator removal is safe and effective [29–31]. Plate or nail fixation at the time of irrigation and debridement is also safe and effective [28,32], but limits the surgeon's ability to re-displace bone ends for wound exploration if repeat debridement is indicated.

Early wound closure or coverage is preferred, as this appears to limit the infection of open fracture wounds [33]. Acute primary closure of open fracture wounds after debridement and fixation, if possible, has been shown to be a safe method of treatment [34]. Early coverage of open fracture wounds that

are unable to be closed primarily has also been shown to be safe and effective [35]. Adjuncts to wound closure, especially in the setting of skin tension, include "pie-crusting" of skin about the wound(s) [36] or performing open wound management with a vessel loop closure technique to re-approximate wound edges [37] and/or use of negative pressure wound dressings [38,39]. Also, if doubts about the safety of closure at the time of initial debridement and fixation persist, then open wound management and repeat debridement are appropriate until closure or coverage is considered safe. This may be a consideration for significantly contaminated wounds at the time of presentation, or open fracture wounds in polytraumatized patients [33]. Negative pressure wound dressings can be utilized successfully for open fracture wounds as a bridge to delayed closure with successful reduction of infection rates in some series [40], or as a bridge to delayed free tissue transfer with reduction of infection rates as compared to traditional dressings [41], perhaps allowing for a possible reduction in need for free tissue transfer [42]. However, this may be a limited process, and earlier wound closure or flap coverage may reduce infection rates over late wound closure or coverage, despite utilization of the negative pressure dressing [43].

An ongoing source of debate in the management of open fractures relates to the timing of debridement. A standard benchmark that has been propagated internationally is that open fractures should undergo urgent irrigation and debridement procedures within 6 hours. However, this benchmark has recently been questioned, as it appears to have little scientific evidence supporting it. In a seminal article on treatment of open fractures, Patzakis and Wilkins demonstrated no relationship between time from injury to surgical debridement of open fractures and subsequent development of infection [14]. A recent prospective, observational study of open fracture patients across eight trauma centers in the United States also failed to show a correlation between time to surgical debridement and the risk of infection of open fracture wounds [44]. Although urgency of treatment for open fractures associated with massive contamination, vascular injury, and/or limb crush is evident, routine emergent management does not appear to be required for open fractures, and after-hours surgery done in a hurried fashion by under-experienced practitioners and teams may result in an increased rate of minor complications [45]. However, it is generally accepted by orthopedic surgeons internationally that open fracture treatment does not represent an elective practice [46].

The polytraumatized patient who sustains high-energy open fractures of the extremities occasionally is a candidate for amputation. Properly indicated, a well-executed amputation can be a life-saving procedure which has the potential to shorten rehabilitation times associated with prolonged reconstruction of the mangled extremity. The debate often centers on whether a limb might be amenable to salvage *versus* amputation at the time of the trauma patient's arrival to the hospital. Errors in judgment regarding this problem have the potential to affect a patient's outcome significantly, both physiologically and psychologically. It should be noted that short-term and intermediate-term outcomes reveal similar levels of disability between limb salvage patients and amputees after major lower extremity trauma [47,48], perhaps indicating that one practice is not routinely better than another. Multiple assessment tools have been developed to assist surgeons with making decisions regarding limb salvage *versus* amputation, including the Mangled Extremity Severity Score (MESS) [49,50] (Table 167.1). However, many of these tools are mediocre at best with regard to their predictive value, as demonstrated by the Lower Extremity Assessment Project (LEAP) [51,52]. A historically held indication for acute amputation in the setting of a mangled extremity, the lack of plantar foot sensation, has been refuted

TABLE 167.1

MANGLED EXTREMITY SEVERITY SCORE (MESS)

Type	Characteristics	Injuries	Points
Skeletal/soft tissue group			
1	Low energy	Stab wound, simple closed fracture, small-caliber GSW	1
2	Medium energy	Open or multilevel fractures, dislocations, moderate crush injury	2
3	High energy	Shotgun blast, high-velocity GSW	3
4	Massive crush	Logging, railroad, oil rig accidents	4
Shock group			
1	Normotensive	BP stable in field and OR	0
2	Transiently hypotensive	BP unstable in field, responsive to IV fluids	1
3	Prolonged hypotension	Systolic BP < 90 in field and unresponsive to IV fluids	2
Ischemia group			
1	None	Pulsatile limb, no sign of ischemia	0[a]
2	Mild	Diminished pulses, no sign of ischemia	1[a]
3	Moderate	No pulse via U/S, sluggish CR, paresthesia, diminished motor	2[a]
4	Advanced	Pulseless, cool, paralyzed, numb limb without CR	3[a]
Age group			
1	< 30 years		0
2	30–50 years		1
3	> 50 years		2

[a]Points × 2 if ischemic time > 6 hours.
Note: MESS equals sum of scores for each of the group types; minimum score is 1, maximum score is 14.
BP, blood pressure; CR, capillary refill; GSW, gunshot wound; IV, intravenous; OR, operating room.
Adapted from Helfet DL, Howey T, Sanders R, et al: Limb salvage versus amputation: preliminary results of the Mangled Extremity Severity Score. *Clin Orthop* 256:80–86, 1990.

by the LEAP study team; many patients presenting with absent plantar foot sensation recovered it completely over time, indicating that the most tibial nerve injuries are neurapraxias (as opposed to complete disruptions) [53]. Ultimately, each injured patient must be carefully scrutinized, and no particular physical examination finding or trauma scale has been shown to be absolutely predictive of the success or failure of attempts at limb salvage. Therefore, thoughtful interpretation of trauma scores is imperative prior to making the choice between salvage and amputation for the mangled extremity in the traumatized patient.

PELVIC FRACTURES

Evaluation

The pelvic ring, functionally, is a rigid ring, despite the fact that it comprises three bones—two hipbones and the sacrum—with three articulations—two sacroiliac joints and the pubic symphysis. It is designed to distribute the weight of the torso, arms, and head onto the legs for normal bipedal ambulation. The pelvis contains the acetabulae, which represent the articulations with the lower extremities, and the lumbosacral junction, representing the articulation with the spine. The sacroiliac joints and pubic symphysis are thought to have minimal motion, and are connected by stout ligaments. In some cases, incompetence of these joints can lead to laxity and chronic pain, which may occur after trauma, complicated vaginal birth in females, or in an idiopathic manner [54,55]. Further ligamentous connection between the posterior and anterior pelvis is provided by the sacrospinous and sacrotuberous ligaments. The transverse processes of the fifth lumbar vertebra are attached to the posterior iliac crests by the iliolumbar ligaments.

Disruption of the pelvic ring in young patients requires a high-energy mechanism, such as a motor vehicle crash or fall from a significant height. As the pelvis functionally is a rigid ring, the discovery of a single break in that ring should prompt careful scrutiny for at least one other break. For example, pubic ramus fractures, in the anterior aspect of the pelvic ring, may be obvious on plain radiographs, but associated sacral fractures may not be readily apparent on plain radiographs due to the overlying bowel gas, radio-opaque contrast agents in the bowel or bladder, or bony anatomy. They may be visible on CT scanning. A high index of suspicion must be maintained. It should also be emphasized that acetabular fractures of a transverse nature (not isolated wall or column fractures) often represent a component of a pelvic ring disruption, and suspicion that such disruption has occurred should be maintained when these acetabular fracture types are present.

Multiple classification schemes exist that describe various aspects of pelvic ring injuries. The Young and Burgess classification is perhaps the most commonly utilized descriptive scheme for pelvic ring injuries, in which they are classified as anteroposterior compression (APC) injuries, lateral compression (LC) injuries, vertical shear (VS) injuries, and "complex patterns" [56]. The Young and Burgess classification can be helpful for identification of other problems that can be associated with the pelvic ring injury, such as increased incidence of head trauma with LC injuries and of abdominal and chest trauma with APC injuries [57], and it can be somewhat predictive of transfusion requirements in trauma patients [58]. Other commonly utilized classification schemes include the Tile classification [59] and the AO/Orthopedic Trauma Association classification [60]. No pelvic fracture classification scheme, however, possesses all seven of the following requisites for universally applicable schemes: ease of use, prognostic value (outcomes), descriptive value (describe the injury), therapeutic value (direct treatment), research value (allows direct comparison between groups), intra-observer reliability, and inter-observer reliability.

Orthopedic examination of the pelvic fracture patient is similar to the orthopedic examination of all polytraumatized patients, covering the entire musculoskeletal system in a methodical manner. Focused examination of the pelvis includes observation of limb deformity; abnormal limb rotation or shortening in the setting of pelvis injury may be secondary either to pelvic deformity or to hip dislocation (with or without associated acetabular fracture), or to extra-pelvic lower extremity fracture. Skin about the pelvis, including about the perineum, must be carefully examined for lacerations that can be associated with open pelvic fractures. Open wounds may be present within folds of skin, and a thorough examination is necessary. Lacerations may lurk within the fold of skin inferior to the scrotum in males, and examination of this area cannot be neglected. Extensive ecchymoses should be noted; these may be indicative of degloving injuries. Digital rectal examination is also required to detect occult open fractures into the rectum, and (chaperoned) vaginal examination is also required in women to detect open fractures violating the vaginal vault. Speculum examination is not generally performed in the trauma bay. Blood emanating from the anus or vagina can be an indicator of open pelvic fracture. Urethral disruptions can also occur with pelvic fracture, and blood at the urethral meatus can be indicative of such an injury. Manual palpation of the pelvis and gentle compression of the iliac crests may detect abnormal motion or crepitus associated with an unstable disruption of the pelvic ring, although this manipulation lacks sensitivity and specificity [61]. Pelvic manipulations must be undertaken judiciously; unstable pelvic ring disruptions can cause life-threatening hemorrhage, which can be exacerbated by repeated examinations. Repeated examinations also can induce severe patient discomfort. A neurovascular examination of both legs, as well as examination of anal sphincter tone and of the bulbocavernosus reflex, is routine.

Standard radiography of the pelvis begins with the anteroposterior view. The inlet radiograph, with the beam tilted approximately 40° caudad, can detect anteroposterior translation of the hemipelvis and rotational hemipelvic deformities. The outlet radiographs, with the beam tilted approximately 40° cephalad, can detect "vertical" translation (more often, a flexion deformity) of the hemipelvis and is useful for visualizing sacral fractures. Judet radiographs, with the patient or x-ray beam tilted approximately 45° to either side, are reserved for patients with acetabular fractures detected on anteroposterior radiographs. Computed tomography (CT) has become routine for polytraumatized patients, and provides extensive information regarding the bony anatomy of a pelvic fracture and/or dislocation. In the setting of pelvic and acetabular fractures, CT scanning is also invaluable for planning of the surgical reconstruction. The CT scan is of limited utility, however, for acetabular fractures if the hip remains dislocated during the scan. Therefore, it is desirable to reduce fracture-dislocations of the hip (acetabulum) prior to CT scanning of the pelvis for adequate delineation of fracture anatomy and for preoperative planning.

Acute Management

Pelvic fracture patients often have multiple associated injuries, all of which may contribute to the overall physiological condition of the patient. Early mortality of patients with pelvic fractures may be related to patient age and occurs as a result of catastrophic hemorrhage, head injury, or multiple organ system

failure [62,63]. As the pelvic fracture may contribute directly to morbidity and mortality, early stabilization is preferred. This stabilization may be performed at the scene of the injury by emergency medical personnel, by the application of a circumferential sheet, pelvic binder, or other compressive garment. Sheets are readily available, inexpensive, and easy to apply [64]. The personnel applying the sheet should do their best to avoid wrinkling the sheet, which may cause skin compromise [65]. Overcompression of the pelvic ring is avoided, as the exact nature of the pelvic injury is unknown; overcompression of certain types of unstable fracture patterns may lead to laceration of the bladder, rectum, vagina, or other intrapelvic structures. Although circumferential pelvic wraps may assist with patient transport and comfort and can successfully reduce some types of pelvic ring disruptions [66], a recent study failed to demonstrate decreases in mortality, transfusion requirements, or the need for pelvic angiography by their use [67].

Upon arrival at the trauma center, all circumferential clothing (including pelvic wraps/binders) is removed to allow for examination of the lower abdomen and pelvis. Binders or wraps can easily be re-applied after examination. Large-bore intravenous access is necessary for fluid resuscitation. Keeping patients warm avoids coagulopathy. Although pelvic fractures may be associated with catastrophic hemorrhage, ongoing hemodynamic instability can arise from a number of causes unrelated to the specific pelvic injury. A full assessment of the patient is required. "Open book" (i.e., anteroposterior compression) injuries of the pelvis can be treated with reapplication of a circumferential wrap. Grossly unstable pelvic injuries can be treated provisionally with the application of skeletal traction, on the same side(s) of the pelvic injury(ies), through either the distal femur or the proximal tibia as the side of pelvic instability. Skeletal traction is also used routinely in the provisional stabilization of acetabular fractures prior to definitive treatment in the operating room; traction can minimize contact of the femoral head with rough acetabular fracture edges.

Pelvic external fixation can be utilized in a resuscitative fashion. External fixator application is difficult, but possible, in the trauma bay. An experienced orthopedic surgeon should perform external fixation of the pelvis, if indicated, to avoid inaccurate pin placement and associated cutout of pins from the iliac crests or injury to the intrapelvic or gluteal structures [68]. Factors that increase difficulty for the application of anteriorly based external fixators can be the rotational deformity and/or instability of one or both hemipelves. Anteriorly based pelvic external fixators are not good at controlling completely unstable posterior pelvic ring disruptions, and reduction of the anterior pelvic ring may be associated with further displacement of the posterior pelvic ring in some circumstances [69]. The antishock "C-clamp" has also been utilized successfully for emergent stabilization of the unstable pelvic ring disruptions [70]. It was designed to be placed posteriorly, with the clamp engaging the posterolateral ilia and exerting compression. The connecting frame can be rotated out of the way to allow for access to the abdomen or perineum. Dangers of application of the C-clamp, especially by inexperienced practitioners, can include fracture and/or penetration of one or both ilia or aberrant placement of one or both ends of the clamp through the greater sciatic notch(es) [71]. The C-clamp has also been applied successfully to the anterior pelvic ring as a resuscitative aid [72].

Patients with pelvic ring disruptions may demonstrate hemodynamic instability that is refractory to volume resuscitation. An ongoing search for sources of blood loss is vital. A recent publication demonstrated that, at a single trauma center, 21% of patients with pelvic fractures and hemodynamic instability (systolic blood pressure < 90 mm Hg) refractory to a 2 L bolus of saline ultimately expired, and 75% of those patients expired as a result of exsanguination [73]. Unstable pelvic fractures are more highly associated with pelvic hemorrhage than are stable pelvic fractures. Therefore, investigation of other potential sources of hemorrhage is vital, especially in the hemodynamically unstable trauma patient with a stable pelvic fracture pattern [74]. Patients with unstable anteroposterior compression injuries have been demonstrated to require massive transfusions, followed by those patients with vertical shear or complex mechanism pelvic ring disruptions, and lastly by those with lateral compression injuries [58,75]. However, fracture pattern may not always be indicative of transfusion requirements or the need for angiographic arterial embolization [76].

The hemodynamically unstable patient with a pelvic ring disruption may have significant fracture-associated hemorrhage. Pelvic fracture-associated bleeding comes from three sources: fracture surfaces, lacerated or ruptured veins, or lacerated or ruptured arteries. Fracture surfaces may not be a source of ongoing massive blood loss, and therefore may contribute negligibly to hemodynamic instability [77]. Distinguishing between major sources of pelvic hemorrhage—arterial or venous—represents a challenging but important task, and prior studies have examined multiple factors that may be associated with successful angiographic embolization, used for arterial hemorrhage, including patient age, trauma scores, shock on arrival to the trauma center, and fracture pattern [78]. Venous hemorrhage after pelvic fracture can be adequately treated with pelvic stabilization, either by circumferential pelvic wrap or by external fixation, while arterial hemorrhage can be addressed with angiographic embolization [79]. Transient response to initial resuscitation, lack of response to provisional pelvic stabilization, and presence of a contrast blush on pelvic CT scanning are all thought to be indicative of arterial hemorrhage that may be amenable to angiographic embolization [80,81].

Pelvic packing has been used for control of severe hemorrhage in hemodynamically unstable patients. It has been proposed that packing may be a more reliable method of treating severe pelvic fracture-associated hemorrhage than angiographic embolization with regard to controlling continued hemorrhage and limiting patient death due to exsanguination [82]. Angiography may also be delayed, and emergency stabilization of the fracture along with or without pelvic packing may be more reliable at controlling severe fracture-associated hemorrhage [83]. Another recent series documented a 30-day survival rate for pelvic fracture patients treated with extraperitoneal pelvic packing of 72%, and subsequent angiography was successful in detecting arterial hemorrhage in 80% of the patients after packing. Immediate increases in systolic blood pressure after packing were also noted [84]. Importantly, both angiography and pelvic packing must be used in a judicious fashion; this will help minimize complications related to both (such as gluteal necrosis).

Genitourinary injuries occur in a small subset of patients with pelvic fracture. This frequency has been shown to approximate 4.6% in a recent study of the U.S.A. National Trauma Data Bank [85]. Another recent study estimated a genitourinary injury rate of 6.8% in pelvic fractures; importantly, 23% of these injuries were missed at the time of initial evaluation [86]. Bladder injuries can also be seen in conjunction with acetabular fractures [87]. Urological injuries most commonly take the form of urethral disruption, extraperitoneal bladder rupture, or intraperitoneal bladder rupture. Diagnosis is often by retrograde cystourethrogram, with careful attention to post-drainage images to detect bladder ruptures not detectable when the bladder is filled with contrast [88]. Urethral disruption appears to occur distal to the urogenital diaphragm, contrary to classical teaching [89]. Primary realignment, when possible, is accomplished endoscopically followed by threading

of the urinary catheter by the Seldinger technique [90]. This repair may be accomplished at the time of pelvic fracture repair, using a team approach [91]. Routine use of suprapubic catheters in the management of urethral disruptions is discouraged, as it may increase the rate of infection, especially in the setting of open reduction and internal fixation of anterior pelvic ring injuries [92]. Bladder injuries are more commonly extraperitoneal. Nearly all present with gross hematuria. Intraperitoneal bladder ruptures are generally treated with surgical exploration, to delineate the extent of injury fully, and with Foley (preferred if open reduction and internal fixation of the pelvic ring fractures will be accomplished) or suprapubic catheters. Extraperitoneal ruptures may be managed with Foley catheters; the bulk of these require no formal repair [93]. However, if open reduction and internal fixation of the pelvic fracture is planned, then primary repair of the extraperitoneal rupture is also accomplished at the same time, with a low infection rate [91]. Use of suprapubic catheters is not required if large-bore Foley catheters are employed after repair of bladder ruptures.

Open pelvic fractures represent a subset of severe injuries with a historically high mortality rate. A recent systematic review calculated the total mortality rate in open pelvic fracture patients across multiple published series prior to 1991 as 30%, and since 1991 as 18%, with the decrease likely owing to aggressive management of the pelvic fracture, selective diversion of the fecal stream, and advances in critical care medicine [94]. These open fractures may be occult, localized within the rectum or vagina. Visual as well as digital exploration is mandatory in these patients. Examination of bowel contents for gross or occult blood is also necessary. Diversion of the fecal stream may be indicated in patients with extensive or posterior wounds associated with their pelvic fractures, but routine use of fecal diversion does not appear to reduce infection rates in patients with open pelvic fractures [95]. Selective fecal diversion, however, does appear beneficial in open pelvic fracture patients with perineal wounds [96].

LONG BONE FRACTURES

Femoral Shaft Fractures

Femoral shaft fractures often occur in conjunction with other injuries after high-velocity blunt or penetrating trauma. Fracture of the femur is associated with significant morbidity in the polytraumatized patient; significant hemorrhage can occur, even in the absence of open wounds. Bilateral femoral shaft fractures are associated with higher mortality rates than are seen in patients with unilateral femoral shaft fractures [97]. Open femoral shaft fractures are unusual and require significant energy to create the situation where the fracture fragment(s) travel(s) through the robust soft tissue envelope of the thigh. Thorough evaluation of any femur fracture patient for associated injuries is necessary.

Initial management of femoral shaft fractures often entails placement of traction devices in the field. These devices are meant to be portable, and they rest against the ischial tuberosity, against which they provide traction through the ankle or the foot. Splinting of femoral shaft fractures is marginally effective at best, as it requires a splint to include the trunk for effective immobilization. The portable traction devices should be removed as quickly as possible to prevent sciatic nerve pressure injury or skin ulceration. Skin or, more commonly, skeletal traction is routinely applied in the emergency department, as a temporizing measure prior to transport to the operating room and to allow for continued evaluation of the patient for other injuries. This traction provides patient comfort, provides immobilization for the fracture, and limits fracture shortening. It can also function as a temporary treatment modality in the setting of operating room unavailability. Evaluation of the patient prior to transport to the operating room should include an investigation of the ipsilateral femoral neck with thorough radiographic imaging. A high percentage of femoral neck fractures are missed in the setting of ipsilateral femoral shaft fractures, and CT scans do not appear to be 100% sensitive for their diagnosis [98].

Operative management is the mainstay of therapy for fractures of the femoral shaft. In the United States, definitive treatment of the femoral shaft fracture patient in skeletal traction is of historical interest only. A distinct advantage of femur fracture stabilization includes the ability to mobilize the patient, thereby avoiding complications associated with prolonged bed rest in critically injured patients, such as pneumonia, pressure ulcers, and deep vein thrombosis. The gold standard for treatment of closed fractures of the femoral shaft is reamed, statically locked, antegrade (from the hip region) medullary nailing. This method of treatment has been demonstrated to be highly effective in numerous studies [99–101], and it can allow for early unprotected weight bearing [102]. Open fractures of the femoral shaft are also effectively treated with medullary nailing, after appropriate irrigation and debridement [10]. Entry portal—piriformis fossa *versus* trochanteric—seems to make little difference in healing rates [101]. Early dynamic locking can be associated with shortening of the fracture, and is generally not utilized in trauma [103]. Retrograde nailing (entry point through the knee) is also effective [104]. Reaming prior to nailing appears to improve healing rates of femoral shaft fractures [105,106], although this may come at the expense of increased pulmonary injury in the setting of chest-injured patients [107].

Other methods of fixation for femoral shaft fractures include open reduction and internal fixation with a plate-and-screw construct and external fixation. Plate fixation is often, but not always, reserved for extremely proximal or extremely distal femoral shaft fractures and for fractures in which intramedullary fixation is contraindicated (e.g., the presence of device, such as a total hip arthroplasty stem, within the femoral canal). Plate fixation has been employed successfully in polytraumatized patients with femoral shaft fractures [108]. External fixation can also be used in the acute setting to stabilize femoral shaft fractures in a minimally invasive and rapid fashion. Although femoral shaft fractures can heal with definitive external fixation, this method of treatment is rarely utilized. Conversion of external fixation to medullary nail fixation for femoral shaft fractures has been demonstrated to be effective and safe [29–31].

Early femoral shaft stabilization is associated with improved outcomes in polytraumatized patients [109]. The method of stabilization is unimportant for these early outcomes; medullary nailing, plate and screw fixation, or external fixation all provide similar benefit. Controversy remains regarding the optimal method of early femur fracture stabilization in the polytraumatized patient, including chest- and head-injured patients. The Hannover group has published extensively regarding the second-hit phenomenon of femoral nailing in polytraumatized patients, and has made recommendations that pulmonary- and head-injured patients perhaps undergo acute "damage-control orthopedic surgery" with external fixation of a femoral shaft fracture, followed by staged conversion from external fixation to medullary nailing when the patient's condition has improved and resuscitation has been completed [107,110–112]. However, some recent studies have demonstrated that reduced rates of acute respiratory distress syndrome (ARDS) can be achieved with acute nailing of femoral shaft fractures, instead of with damage control orthopedics, in polytraumatized patients [113–115]. Adequate resuscitation

has been shown to be important prior to nailing [114]. Also, the utilization of reaming has been shown not to create increased rates of ARDS in polytraumatized patients undergoing medullary nailing of femur fractures, as compared to patients undergoing nailing without reaming [114].

Tibial Shaft Fractures

Fractures of the tibial shaft are very common in polytraumatized individuals and after high-velocity trauma. Tibial fractures have a higher likelihood of being open [116,117], perhaps secondary to the thin soft tissue envelope surrounding the human tibia. This soft tissue envelope may also play a role in the increased likelihood of infection and nonunion for tibial fractures treated operatively; infected nonunion is more common after tibial fracture than after any other fracture of a long bone [118]. Compartment syndrome is also common after high-energy fractures of the tibia, even when the fractures are open [10].

Principles of treatment of tibial shaft fractures are similar to those of femoral shaft fractures; to provide comfort, restore length, alignment, and rotation, and allow for early mobilization. Tibial fractures are commonly treated with medullary nailing techniques, unless there are fracture extensions into the knee and/or ankle joint. Nailing of tibia fractures can provide sufficient stability to allow for full weight bearing after surgery [119]. Plating of tibia fractures is more often done for those fractures with involvement of the articular surfaces of the tibia, and normally weight bearing is restricted in those patients until some evidence of radiographic healing is present. External fixation is most often utilized in a temporary fashion, especially with large open wounds requiring repeat debridement, in complex fractures involving the tibial plateau or tibial plafond, or in patients with significant physiological instability. Conversion of external fixation to nailing is safe, when the patient's condition permits [30,31].

Tibia fractures in patients sustaining multisystem trauma can be stabilized in a delayed fashion, after the physiological condition of the patient has improved. Unlike femoral shaft fractures, tibia fractures can be effectively treated temporarily with long-leg splints. This allows for patients to be gotten out of bed and to sit up in bed or a chair, with improvements in pulmonary function. However, splinted tibia fractures must be carefully monitored for skin breakdown from the splinting material, compartment syndrome, and impending skin compromise from unstable fracture ends.

Humeral Shaft Fractures

Fractures of the humeral shaft are a source of morbidity in polytraumatized patients. They have implications for early rehabilitation as well as for future function. Injuries associated with humeral shaft fractures that have profound consequences on outcomes include brachial artery injuries and nerve injuries; the radial nerve is particularly susceptible to concomitant injury with humeral shaft fracture. Management of humeral shaft fractures and their sequelae are based upon the overall condition of the patient and on the personality of the injury.

Humeral shaft fractures, when they occur in isolation, are particularly amenable to closed management. Splinting, casting, and fracture bracing have all been noted to be highly successful in achieving union of humerus fractures [120,121], and long-term outcomes (at a minimum of 1 year) are thought to be as good as those after surgical repair [122]. Critically, these results were obtained in isolated humeral shaft fractures. Considerations for the management of humerus fractures in polytraumatized patients, however, likely are different.

Polytraumatized patients often require the use of both arms for effective mobilization and rehabilitation. They often are subjected to prolonged bed rest, and may be incapable of the frequent fracture brace adjustment that is advocated by Sarmiento and colleagues [120]. As fracture braces are not generally utilized in the acute phase after fracture (delay of 1 to 3 weeks prior to application is common), early splints can be cumbersome for patients and caregivers, can be unwieldy, and are not generally removable for the purposes of skin monitoring and vascular access. Obtunded patients also cannot complain about pressure points beneath a non-removable splint, and they do not routinely change position in an effort to alleviate pressure points. Skin necrosis can be a danger in this setting. For all of these reasons, management of humeral shaft fractures in polytraumatized patients is normally operative.

Humerus fractures can be treated either with open reduction and internal fixation, utilizing a plate-and-screw construct, or with medullary nailing. Advocates of plate-and-screw fixation cite the ability of humeral shaft fracture patients to utilize their arms for assistance with ambulation (i.e., weight-bearing on crutches or a walker) after fixation [123]. Advocates of medullary nailing for humeral shaft fractures have demonstrated good outcomes [124], although no literature exists that provides evidence regarding immediate weight bearing after nailing of humerus fractures. Some literature exists that appears to favor plating *versus* nailing for humeral shaft fractures, as shoulder impingement and reoperation risk appear to be lower with plating [125–127], although a definitive answer regarding optimal surgical treatment of humeral shaft fractures is not available. In the setting of radial nerve palsy, present between 8% and 11% of the time [128,129], nerve exploration can also occur at the time of surgery. However, radial nerve palsy is not an indication for operative exploration of the nerve [130]; the bulk of radial nerve palsies appear to be neurapraxias, and a recent study reported that 89% recover normal distal neurological function after closed humeral shaft fracture management [131]. Even secondary radial nerve palsies (those occurring later, such as after fracture manipulation) appear to have a high rate of complete recovery despite nonoperative management [129].

Forearm Fractures

Forearm fractures, while not often a contributing factor to mortality in the polytraumatized patient, are a source of long-term morbidity if not properly addressed. The forearm functions as a mobile unit which is dependent upon the anatomy of the radius and the ulna. The radius and ulna are "parallel" but curved bones, and this anatomy is vital for the maintenance of proper forearm rotation (pronation and supination). The maximal radial bow has been shown, in anatomical studies, to be approximately 16 mm and located near the junction between the middle and distal one thirds of the forearm length [132]. Encroachment of either bone or of foreign material into this region may have adverse consequences on forearm rotation, and may create limitations of pronation, supination, or both.

Fracture of one bone of the adult forearm often leads to injury associated with the other bone, whether it is fracture or dislocation of the other bone, with dislocation of the other bone; dislocation, when it occurs, is either at the elbow (radius) or wrist (ulna). The anatomical connections between the radius and ulna include the proximal and distal radioulnar joints and the interosseous ligaments; deformation of one bone, due to fracture, that is not "compensated" by fracture of the other bone will cause the other bone to be drawn in the direction of the deformation, causing dislocation. Typical patterns include displaced proximal ulnar shaft fractures associated with dislocations of the radial head from the capitellum

(the "Monteggia" fracture–dislocation) and displaced distal radial shaft fractures associated with dislocations of the ulnar head from the distal radioulnar joint (the "Galeazzi" fracture–dislocation).

Careful scrutiny of the elbow, forearm, and wrist is vital for the detection of these injuries, which may be overlooked in the setting of multiple trauma. Failure to recognize these injuries acutely can result in increased difficulty with surgical reconstruction (if accomplished late) or significant disability (if reconstruction is never accomplished). Forearm fractures tend to shorten, due to the powerful investing musculature of the forearm, and surgical repair is often more straightforward when it can be undertaken within a few days of injury. Perfect anatomical reconstruction is associated with the best outcomes. Early motion is encouraged to minimize the likelihood of excessive bone formation within the injured tissues between the radius and ulna, which can lead to encroachment of the two bones and restriction of forearm rotation. The repaired forearm is often protected and weight bearing is restricted for a number of weeks. However, "platform" walkers or crutches may be utilized for assistance with ambulation in many cases; the weight of assisted ambulation is borne through the elbow (as opposed to the wrist and forearm) with these devices.

Although forearm fractures may not be a direct cause of early mortality in most patients who succumb to the sequelae of severe trauma, it can be a contributing factor. Forearm fractures can result in lacerations of the ulnar and/or radial arteries, which can contribute to blood loss. Forearm compartment syndrome can also develop in the patient with severe forearm fractures; unrecognized compartment syndrome can result in myonecrosis with resultant myoglobinuria and potential contribution to renal insufficiency (see below), let alone future disability. Open fractures of the forearm should not be thought to decompress the compartments of the forearm adequately; a heightened index of suspicion of compartment syndrome should be maintained in all patients with high-energy fractures of the forearm, whether they are closed or open fractures.

COMPARTMENT SYNDROME

Muscle groups are divided into compartments by layers of fascia, which are noncompliant. Injury to a particular muscular compartment can induce edema and/or hemorrhage within the compartment, leading to increased intracompartmental pressures due to the noncompliant nature of the surrounding fascia. Increased intracompartmental pressure can lead to venous congestion and resultant muscle ischemia within the involved compartment(s). This scenario is termed "compartment syndrome." As nerves traverse the muscular compartments, they are also susceptible to compartment pressure-related compromise.

The absolute intracompartmental pressure at which a compartment syndrome exists continues to be a matter of debate. Some authors have previously advocated threshold intracompartmental pressures, such as absolute values of 30 mm Hg or 40 mm Hg, as diagnostic of compartment syndrome. However, a differential between intracompartmental pressure and diastolic blood pressure is thought to be a more reliable indicator of evolving compartment syndrome. The pressure differential (referred to as ΔP or "delta-P") thought to be diagnostic of compartment syndrome is commonly accepted to be 30 mm Hg or less [133]. The improved reliability of ΔP measurements, as opposed to absolute measurements of intracompartmental pressures alone, was recently illustrated in a series of 101 tibial fracture patients. In this series, 41 patients had continuous leg intramuscular compartment pressures more than 30 mm Hg for over 6 hours in the setting of a satisfactory ΔP (defined as $\geq$30 mm Hg). No difference in outcome regarding return to function and muscle strength was noted, as compared to a control group of 60 patients without elevated intramuscular pressures [134].

The number of muscle compartments is variable based upon location in the body. The brachium has two muscular compartments (anterior and posterior), the forearm has three muscular compartments (dorsal, volar, and mobile wad), the thigh has three muscular compartments (anterior, posterior, and adductor), and the leg has four muscular compartments (anterior, lateral, superficial posterior, and deep posterior). The exact number of muscular compartments in the hand and the foot are a matter of debate. Hand compartments include the interosseous compartments as well as the thenar and hypothenar compartments, and foot compartments include the interosseous compartments as well as the abductor and adductor compartments. The gluteal muscles are also contained within fascial compartments, and gluteal compartment syndromes have been documented in obtunded trauma patients as well as intoxicated patients (and others with an altered level of consciousness), with the gluteal muscles in a dependent position, who do not change their position for an extended period of time [135].

Compartment syndrome is a problem that can arise in polytraumatized patients who have sustained high-energy injuries. Younger patients may be more susceptible [136]. Typical injuries associated with development of compartment syndrome include fractures, dislocations, crush injuries, and prolonged episodes of limb ischemia. The syndrome can also develop after reperfusion of a dysvascular limb that occurs after a revascularization procedure or simply after a manipulative reduction of a fracture that reduces kinking and occlusion of vessels. Isolated soft-tissue injury (without fracture) was the second most common cause of compartment syndrome in a large series of patients reviewed over an eight-year period [137]. Another study examined a cohort of 38 patients without fracture who developed compartment syndrome at a single trauma unit in Great Britain. Frank muscle necrosis was noted in 20% of patients without fracture, as compared to 8% of patients with fracture, indicating that a high index of suspicion for compartment syndrome in trauma patients must be maintained, even in patients without fractures [138]. Penetrating injuries, such as gunshot and stab wounds, can lacerate arteries within a single compartment or multiple compartments, leading to hemorrhage under pressure into a confined environment and creating a compartment syndrome. The presence of a penetrating injury or open fracture (which results in fascial disruption) should not create a false sense that compartment syndrome will not develop; compartment syndromes have been documented to occur in the setting of penetrating injury or open fracture [139].

Compartment syndrome can also develop after stabilization of a fracture, such as after nailing a tibia fracture, once the compartment has been returned to its pre-injury length and its available volume is thereby diminished. This "finger-trap" phenomenon was initially described in the literature by Matsen and Clawson [140]. More recent mathematical and experimental analyses indicate that the available volume within a given muscular compartment varies inversely with acute changes in the length of the limb [141]. Tibial traction or fracture reduction in the setting of tibial shaft fractures raises compartment pressures [142]. A fracture situation in which excessive shortening is corrected, or vigorous traction is required to maintain reduction, should perhaps prompt increased vigilance for the development of compartment syndrome. This risk must be balanced, however, during staged management of severe fractures, as the consequence of initial inadequate limb-length restoration may be increased difficulty of the definitive reconstructive procedure at the time of formal open reduction and internal fixation. Also, a recent report revealed that in tibial plateau fractures, application of an external fixator device which spans

the knee and fracture may lead to transient elevations of intracompartmental pressure, but does not appear to cause a compartment syndrome [143].

Missed compartment syndromes can lead to significant morbidity. Frank muscle necrosis is a normal sequela of compartment syndrome, and associated joint contractures have been extensively described in the literature. Elevated levels of serum creatine phosphokinase (CPK) or the appearance of myoglobinuria (which can be misinterpreted as hematuria) are associated with muscle necrosis, and have been utilized in the past as diagnostic tools for evolving compartment syndromes [144,145]. Delayed treatment of compartment syndrome is fraught with complications [146]. Infection rates are dramatically increased when fasciotomy for compartment syndrome is delayed [147]. Fasciotomy revision, performed in a delayed fashion for inadequate index fasciotomy (and failure to relieve compartment syndrome), has been associated with increased rates of mortality and major amputation [148]. Often, it is not possible to determine the exact time of onset for a compartment syndrome. Therefore, the recommendation is that fasciotomy be undertaken as expeditiously as possible after diagnosis of compartment syndrome, and that a high index of suspicion for the development of compartment syndrome should be maintained in patients with high-energy trauma or trauma patients who are obtunded.

Compartment syndromes should be diagnosed during the evolution phase. A high clinical suspicion should be maintained in any patient who has sustained a high-energy injury. Pain out of proportion to the injury should alert the examiner to the possibility of impending compartment syndrome. Orthopedic injuries are very painful by their nature, and patients often have differing pain tolerances (sometimes affected by chronic narcotic use/abuse), so the examiner should be sensitive to *changes* in pain level as reported by the injured patient. Traditionally, the "five P's" have been utilized in the awake, responsive patient for examination of the leg and ruling out compartment syndrome: pain with palpation of the compartment, pallor, paresthesia, pain with passive stretch, and pulselessness are commonly quoted as signs of compartment syndrome. Pulselessness should not be included in this list, as it requires excessive pressures to occlude arteries–in excess of systolic pressure–and should this scenario arise, it would likely be associated with complete myonecrosis within compartments involved. Excessive pain with passive stretch of muscles within each compartment should alert the examiner to evolving compartment syndrome. Awareness of the patient's injuries and their direct contribution to pain with the motion of a joint (e.g., intra-articular fracture) should be considered. All compartments in a traumatized extremity should be examined. Muscle compartments tend to be very firm in the setting of evolving compartment syndrome.

Direct monitoring of intracompartmental pressure is possible utilizing the wick catheter technique, an arterial pressure line setup, or a variety of commercially available devices. These methods provide direct measurements of intracompartmental pressures in mm Hg. It should be emphasized, however, that compartment syndrome is primarily a diagnosis based upon physical examination. Physical examination findings consistent with evolving compartment syndrome should prompt surgical intervention, even in the setting of compartment pressure measurements that indicate normal ΔP, as the consequences of missed compartment syndrome include frank myonecrosis and irreversible neurological injury. Complete reliance upon direct intracompartmental measurements may result in undertreatment or overtreatment of compartment syndrome. Intracompartmental pressure measurements have been shown to be highest within 5 cm of fracture, and measurements taken outside of this zone may be spuriously low and lead to undertreatment [149]. Also, there is a documented decrease in diastolic blood pressure after induction of general anesthesia; intracompartmental pressure measurements obtained in a patient under anesthetic must be interpreted cautiously as the ΔP value may be spuriously low and lead to overtreatment [150]. Diagnosis of compartment syndrome is variably difficult, even at large trauma centers [151], and high indices of suspicion need to be maintained to prevent undertreatment (and overtreatment) of compartment syndromes.

Obtunded patients should be monitored serially. The examiner should note compartment firmness and proceed appropriately. Significant degrees of subcutaneous edema can mask tense compartments. Compartment pressure monitoring with commercially available devices or with an arterial pressure line setup may be utilized for diagnosis in the obtunded patient, especially if the patient exhibits no response to painful stimuli and if physical examination of compartment tightness is impeded by extensive surrounding edema (e.g., with anasarca).

Open fractures do not necessarily decompress compartments through which the fracture fragments or projectiles have penetrated. An approximately 9% rate of compartment syndrome has been reported with open fractures of the tibial shaft [139]. The degree of soft tissue injury appeared to be directly proportional to the incidence of compartment syndrome in this population. Therefore, compartment syndrome should be suspected in all patients with appropriate symptomatology, and the presence of open wounds does not negate the possibility that compartment syndrome may be evolving.

Techniques of fasciotomy have been described extensively. Adequate decompression of all compartments in the affected portion of the extremity is the goal. During fasciotomy, nonviable muscle is debrided. Following fasciotomy, closure of the fascia is not indicated (this would re-create the compartment syndrome). Skin closure should be undertaken cautiously. Use of vessel loops to assist with skin reapproximation has been described [152]. Negative-pressure wound therapy devices may also be beneficial in promoting growth of granulation tissue on a fasciotomy bed, in anticipation of skin grafting, or in maintaining smaller wound dimensions, in anticipation of delayed primary closure [153,154]. Most fasciotomy patients will require return to the operating room for further irrigation and debridement procedures, followed by delayed primary skin closure or skin grafting.

The greatest risk of fasciotomy in patients with evolving compartment syndrome is incomplete fasciotomy technique. It is imperative to verify that all compartments in the affected extremity have been released, regardless of surgical approach utilized. Anatomy may be distorted due to fracture deformity, excessive hematoma, or soft tissue avulsion, and it occasionally can be difficult to discern fascial planes. Also, visualization can be impaired by "minimally invasive" or "cosmetic" incisions, and therefore it is inappropriate to perform fasciotomy in the urgent to emergent situation on a traumatized extremity through anything but full-length incisions. Small incisions for fasciotomy are described and often are used for the treatment of exertional compartment syndrome, but their utility in trauma is questionable at best. Visual verification of complete release of all four compartments should be made prior to the initiation of wound closure and departure from the operating room.

Fasciotomy can be associated with both acute and long-term morbidity. Multiple neurovascular structures can be injured during fasciotomy. Risk can be minimized by careful and meticulous dissection technique, maintaining nerves and vessels within a cutaneous flap (if possible), and assuring that neither is directly exposed to the environment (dressing) at the conclusion of the case. At least one case of profound hemorrhage after erosion of an artery beneath a negative-pressure wound therapy device has been reported [155]. Analysis of long-term outcomes related to fasciotomy is difficult in the

trauma setting due to the concomitant injuries that have invariably occurred and which can have an effect upon function. Nevertheless, a retrospective analysis of 40 patients undergoing leg fasciotomy for a variety of reasons has been published [156]. Complications of leg fasciotomy were common, and included neurological injury in 15%, hemorrhage in 35%, and infection in 25%. Only 45% of legs healed with a good functional result, and 27.5% had a severely disabled leg at the time of final healing. Five of the patients (12.5%) ultimately required ipsilateral leg amputation, and six patients (15%) expired. Another report indicated frequent patient complaints related to fasciotomy wounds, including decreased sensation, tethering of tendons, and recurrent ulceration [157]. Other known side effects of compartment release include pruritus, reflex sympathetic dystrophy, temperature sensitivity, venous stasis, and chronic edema. Despite these concerns, the morbidity and potential mortality of an untreated compartment syndrome is likely to be much higher. Also, a number of published reports, reviewed by Bong et al. [158], indicate that outcomes of fasciotomy for chronic exertional compartment syndrome (in the absence of trauma) are reliably good. These reports, however, require cautious interpretation for their application to trauma, as they did not include patients who required fasciotomy for trauma-related compartment syndrome.

OTHER SEQUELAE OF ORTHOPEDIC TRAUMA

Deep Venous Thrombosis

Polytraumatized patients with lower extremity or pelvic fractures often are subjected to prolonged periods of immobilization or reduced mobility. They are at risk for development of deep venous thrombosis (DVT) and subsequent pulmonary thromboembolism (PE). Management of the orthopedic trauma patient must take into account the increased propensity for these patients to develop venous thromboembolic disease.

There has been much debate in the literature about appropriate methods of DVT prophylaxis in orthopedic trauma patients. The Eastern Association for the Surgery of Trauma (EAST) states that the greatest risk factors in trauma patients for development of venous thromboembolism (VTE) are spinal fractures and spinal cord injury. They also state that insufficient evidence exists regarding risk of VTE in trauma patients as it relates directly to long bone fracture or pelvic fracture [159]. Trauma patients with pelvic and acetabular fractures are thought to have an increased risk of VTE [160]. However, there is little evidence in the literature, apart from observational studies, regarding the best method of DVT prophylaxis for pelvic and acetabular fracture patients [161].

Prophylaxis of trauma patients, especially those with pelvic and acetabular fractures, is important to reduce the risk of DVT. Trauma patients have been shown to have lower rates of DVT when both chemical and mechanical means of prophylaxis are utilized [162]. Mechanical DVT prophylaxis can consist of foot pumps or pneumatic compression devices. Continuous passive motion for the knee in the injured extremity has also been shown to be helpful [163]. Chemical DVT prophylaxis often consists of low-molecular-weight heparin (LMWH) in hospital inpatients; warfarin is not commonly used acutely in the trauma patient (although it may be utilized for longer-term DVT prophylaxis when indicated). In patients thought to be at higher risk of VTE and who are awaiting surgical intervention for fracture repair, chemical prophylaxis does not need to be halted in anticipation of surgery [164]. Despite adequate prophylaxis, however, patients are still at risk for development of DVT [165].

Patients with pelvic, acetabular, and proximal femoral (hip) fractures are at risk of development of VTE [160]. Fractures below the hip are associated with lower risk of DVT; 8% of patients with below-the-hip fractures were demonstrated in one study to develop DVT [166]. Fractures below the knee (i.e., tibia, ankle, foot) do not seem to elevate the risk of VTE significantly; low rates of DVT have been found in patients with ankle fractures treated with cast immobilization [167], and a recent study demonstrated that DVT prophylaxis was of limited to no benefit in patients with fractures below the knee [168].

Routine screening for the presence of DVT in trauma patients is not commonly done. Methods of detecting DVT include compression Doppler ultrasound and venography. In patients with pelvic and acetabular fracture, known to be at a higher risk for DVT than other patients with lower extremity fractures, venography has not been shown to be an effective screening tool [169]. In general, routine screening for DVT is ineffective in trauma patients with pelvic and acetabular fractures, as demonstrated in a recent review of 973 patients [170].

Peripheral Nerve Injury

The bulk of peripheral nerve injuries that occur as a consequence of trauma are neurapraxias, which often will recover with time. Typical neurological injuries include radial nerve palsies in association with humeral shaft fractures, sciatic nerve palsies (peroneal branch, in particular) in association with pelvic and acetabular fractures, and brachial plexopathies in association with scapulothoracic dissociation.

Radial nerve palsies occur after approximately 12% of humeral shaft fractures [129]. An early description of radial nerve palsy in association with humeral shaft fracture was published by Holstein and Lewis, and describes the association with a spiral fracture of the humeral shaft located at the junction between the middle and distal one thirds of the diaphysis [171]. However, some more recent research has called the relationship between this particular humerus fracture pattern and radial nerve palsy into question [129]. The radial nerve supplies motor innervation to the extensors of the hand and wrist; patients with radial nerve motor palsies will lack the ability to extend the wrist or hyperextend the interphalangeal joint of the thumb, which is mediated by the extensor pollicis longus. The extensor digitorum communis (EDC), also supplied by the radial nerve, extends the metacarpophalangeal joints of the hand, but patients may recruit other muscles or perform other functions (such as wrist flexion) that will serve to extend the digits, even though the EDC is not functional. The interphalangeal joints of the fingers (index, long, ring, small) are extended by the intrinsic muscles of the hand, which are innervated by the median and ulnar nerves, and therefore are not affected by radial nerve palsy. Radial nerve-mediated sensation includes the dorsal surfaces of the forearm and hand; the most specific location for radial nerve sensation is the dorsum of the first web space on the hand.

Most radial nerve palsies are thought to be traction injuries (neurapraxias), as opposed to complete disruptions (neurotmesis) or impalings on bone edges [172]. Rarely, the radial nerve may become entrapped within the humeral fracture site, creating neurological deficits [129]. In the setting of high-velocity penetrating injury (gunshot wounds), a radial nerve palsy may be secondary to blast effect of the projectile (as opposed to nerve transaction). Radial nerve palsy at presentation in a patient with a humeral shaft fracture is not considered an indication for surgery, either for nerve exploration or humeral shaft fracture fixation. In the past, humeral shaft fracture

patients presenting with intact radial nerve function which then is lost after manipulation of the fracture (e.g., for reduction) was considered an indication for operative nerve exploration; it has been shown, however, that the bulk of these "iatrogenic" radial nerve palsies resolve on their own, with no residual deficit, and that fracture fixation or nerve exploration is not indicated in these patients either [129]. Humeral shaft fracture fixation should be undertaken in patients who would benefit (or who specifically request fixation), after thorough risk and benefit discussions with the patients and/or their families, and should not be prompted by the presence of a radial nerve deficit. Electromyography and nerve conduction studies are not helpful in the acute setting, and have low sensitivity and specificity regarding the etiology of radial nerve palsy immediately after injury. Ultrasonic examination, however, can be beneficial to detect nerve laceration or entrapment, when utilized by experienced practitioners [173].

Although radial nerve palsies are most often transient, their recovery can take many weeks to months. During this time, flexion contractures of the wrist and digits can occur. Splinting and occupational therapy, with daily manual stretching exercises, are beneficial to minimize this problem. Electromyography and nerve conduction studies may be performed between 6 and 12 weeks following the onset of the radial nerve palsy if there has been absolutely no recovery of function after the injury [172]. Functional recovery is slow; rapid recovery should not be expected. A good rule of thumb is that nerve recovery progresses at approximately 1 mm per day [174]. Therefore, an injury to the radial nerve at the midshaft of the humerus should be expected to result in dorsal hand sensory deficits for many weeks.

Sciatic nerve palsies can occur in conjunction with pelvic or acetabular fractures. Acetabular fractures with posterior dislocation of the hip have an association with the development of sciatic nerve palsy [175]. Pelvic or acetabular fractures, with extensions of fracture lines into the sciatic buttress at the greater sciatic notch, can result in direct laceration of the sciatic nerve; this pattern of fracture can also result in catastrophic hemorrhage due to laceration of the superior and/or inferior gluteal arteries. Pelvic ring disruptions, with wide displacement of the hemipelvis, can also cause sciatic nerve palsies or lumbosacral plexopathies [176], perhaps due either to avulsion of nerve roots or to neurapraxia [177,178]. Nerve roots may be lacerated in association with sacral fractures [179]. The peroneal division of the sciatic nerve is more commonly affected than the tibial division [180]; it has been postulated that this has to do with more points at which the peroneal nerves are tethered down the lower extremity than the tibial nerves.

The bulk of sciatic nerve palsies are also neurapraxias [177]. Prognosis of these, however, is poorer than that for radial nerve palsy, perhaps secondary to the long distance across which recovery must occur (the nerve bud must travel from the pelvis to at least the superior leg, where innervation of the peroneal muscles and ankle and toe dorsiflexors occurs) [180]. Electromyography and nerve conduction studies are useful for characterizing the injury, and many patients with mild injuries regain good function [181].

Scapulothoracic dissociation, likened to a closed forequarter amputation [182], occurs when the shoulder girdle and upper extremity are pulled away from the midline [183]. Prompt recognition of this injury complex is vital. Significant degrees of scapulothoracic dissociation can result in the rupture of subclavian or axillary vessels [182,184]. The injury complex can have devastating effects upon the neurological function of the upper extremity, due to the stretch of nerves or brachial plexus, or due to the avulsion of nerve roots from the cervical spine [182]. Degree of neurological injury and prognosis for recovery correlates with the location of vascular injury; more proximal vascular injury correlates with more severe neurological compromise and poorer prognosis [185]. Evidence of expanding hematoma within the axilla of a patient with such an injury should prompt emergent vascular surgical consultation. Careful attention to the vascular status of the distal upper extremity must be paid to any patient with a distracted clavicular fracture, a significantly-displaced scapular fracture, or a clear increase in distance on anteroposterior chest radiograph between the thoracic spine and the medial border of the scapula, known as the scapular index [186]. Computed tomography is of questionable benefit for initial diagnosis, as the axis of the beam may not be perfectly perpendicular to the axial skeleton, and therefore determination of scapular index may be unreliable. Recovery of brachial plexus function after scapulothoracic dissociation is unreliable at best, especially after nerve root avulsion [184,185,187].

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DAVID A. DRACHMAN · DAVID PAYDARFAR

CHAPTER 168 ■ AN APPROACH TO NEUROLOGIC PROBLEMS IN THE INTENSIVE CARE UNIT

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Neurologic problems present in the intensive care unit (ICU) in two modes: (a) primary neurologic problems, usually under the care of a neurologist or neurosurgeon, and (b) secondary neurologic complications, occurring in patients with other medical or surgical disorders. Only a handful of common clinical situations bring neurologists and patients together in the ICU, although they may be caused by myriad disease states [1]. These situations include:

1. Depressed state of consciousness; coma
2. Altered mental function
3. Required support of respirations or other vital functions
4. Monitoring of increased intracranial pressure (ICP), respirations, state of consciousness
5. Determination of brain death
6. Prevention of further damage to the central nervous system
7. Management of seizures or status epilepticus
8. Evaluation of a neurologic disease that occurs in the course of a severe medical disease
9. Management of a severe medical disease that develops in the course of a neurologic illness

Patients with primary neurologic problems most commonly have conditions with an identified cause, such as stroke, seizures, Guillain-Barré syndrome, head trauma, or myasthenia gravis. Such patients are admitted to the ICU for close observation and management of vital functions, such as respiration, control of ICP, or arrest of seizure activity. These patients represent the minority of neurologic problems seen in the ICU. Far more frequently the neurologist is called on to evaluate the neurologic complications of medical disease: impairment of consciousness in a patient who has undergone cardiopulmonary resuscitation, development of delirium in an elderly individual with a serious infection, or occurrence of focal neurologic deficits in a patient with a ponderous medical record that reveals long-standing diabetes, renal failure, hypertension, and pulmonary disease.

The questions posed to the neurologic consultant are often imperfectly framed. Background observations regarding the origin, onset, and course of the neurologic abnormality may be unavoidably sparse and the history unavailable. The classic neurologic methodology, which involves a comprehensive history and meticulous examination, is rarely possible in patients encumbered with endotracheal tubes, cardiac monitors, and indwelling arterial and venous lines. For these reasons, neurologists must adopt special strategies to function effectively in the ICU, focusing sharply on the specific question with which they are dealing.

INDICATIONS FOR NEUROLOGIC CONSULTATION IN THE INTENSIVE CARE UNIT

Depressed State of Consciousness

The patient with the most common of ICU neurologic problems—a depressed state of consciousness, ranging from lethargy to coma—raises a host of questions. Does the patient have a focal brainstem lesion or diffuse cerebral involvement? Is there an anatomic lesion or a metabolic disorder? Have vital brainstem functions been impaired? Is ICP increased?

The most common primary neurologic causes of depressed consciousness include head trauma, intracranial hemorrhage, post cardiac arrest anoxia-ischemia, and less commonly, inapparent seizures. The secondary conditions seen most often are metabolic, such as anoxia, drug intoxication, or diabetic acidosis. Sometimes the diagnosis is evident, as in head trauma; other times determination of the cause of depressed consciousness may present a diagnostic challenge, demanding a race against the clock to avoid irreversible changes. In every case, it is crucial to establish whether depressed consciousness is due to intrinsic brainstem damage, increased ICP, toxins, widespread anoxia or ischemia, or some other less common cause. It is particularly important to sort out rapidly the component(s) that may be treatable.

Examination of the patient with depressed consciousness exemplifies some of the difficulties of neurologic care in the ICU. Details of this examination are described elsewhere [2]. Like the standard neurologic examination, however, it includes evaluation of mental status, cranial nerve functions, motor functions and coordination, reflexes, sensation, and vascular integrity. The observations made must be used to answer the questions posed above, supplemented by appropriate laboratory studies when possible.

A detailed evaluation of memory and cognitive function is rarely possible in patients who are lethargic, and never possible in those who are stuporous or comatose. Instead, the physician must estimate the patient's responsiveness. Can the patient say any words or respond to commands? Does the patient open his or her eyes? Does the patient groan in response to a painful stimulus or attempt to remove it in a purposeful way? What is the status of the vital functions? Is the respiratory pattern disturbed? The Glasgow Coma Scale score is a simple, but useful, way to document the patient's sensorium [3].

Cranial nerve evaluations include determination of vision, done by observing how the patient follows a large object or a light, gazes toward right and left visual fields, or blinks to a visual threat. Pupillary size, equality, and responsiveness to light

are assessed. Corneal reflexes, cough, and vibrissal (nasal) reflexes are evaluated. "Doll's eyes" (vestibulo-ocular) responses are determined by rotation of the head from side to side; if they are absent, ice water caloric testing can be carried out. Facial movements are assessed in response to painful supraorbital stimuli; the gag reflex is tested in the usual fashion.

Motor function is evaluated as completely as possible. All limbs are observed for spontaneous movement and symmetry as well as tremor or other adventitious movements. If no spontaneous movements take place, a pinch or other noxious stimulus can be used to observe purposeful defensive movements. Decerebrate (i.e., four-limb extensor) and decorticate (i.e., upper limbs flexor, lower limbs extensor) rigidity are observed. Tone is assessed passively for spasticity or rigidity. Deep tendon reflexes are checked in the usual way, working around restraints and intravenous tubing. Grasp, suck, snout, and plantar reflexes are evaluated.

Pain is often the only sensory modality that can be tested. The physician must determine whether withdrawal from pinch or pinprick is appropriately defensive or (in the lower extremities) merely part of an exaggerated extensor–plantar response with triple flexion (flexion at hip, knee, and great toe), which may be mistaken for purposeful withdrawal. Finally, the vascular status is evaluated by listening for bruits over the carotid and subclavian arteries, the vertebral arteries, and the orbits.

Such an examination reveals the patient's state of consciousness, the integrity of brainstem reflexes, and the presence or absence of lateralizing or focal neurologic deficits. The value of the systematic (if limited) neurologic examination cannot be overestimated. For example, in a comatose patient, the finding of decerebrate rigidity that points to significant damage at the level of the pons may be more valuable than many laboratory studies, and unilateral weakness of limbs with ipsilateral hyperreflexia indicates a focal brain disorder rather than a diffuse metabolic problem.

Neurodiagnostic studies are often critical in the analysis of comatose patients in the ICU, but the patient's immobility and dependence on life support systems present special difficulties. A neuroradiology suite that is distant from the ICU presents additional obstacles. It is frequently difficult to obtain a magnetic resonance imaging scan, computed tomographic scan, or arteriogram on a patient who is dependent on a respirator. Paradoxically, in patients with the most urgent problems, it is often least convenient to obtain the maximum amount of neurodiagnostic information. The decision that a patient is too sick to have the crucial study performed is often incorrect. In such desperate cases, risks must be taken to obtain life-saving information.

Management of the patient with depressed consciousness depends largely on the cause. Techniques for eliminating toxins, reducing ICP, and maintaining vital functions must be applied, depending on the diagnostic context (see Chapter 169).

Altered Mental Function

In patients who remain relatively alert, other organic disorders may affect mental function, producing an often perplexing variety of clinical patterns. These include confusion, delirium, aphasia, and isolated memory impairment. The first question for the physician is whether the patient's abnormal mental function represents a recent change that is part of the present illness, or instead is part of a long-standing problem. It is also critical to note whether the change developed abruptly (e.g., after surgery or cardiac arrest) or if there is no known precipitating event; and whether it is improving, worsening, or stable.

Confusion and delirium are commonly reversible and generally result from metabolic and toxic disorders (see Chapters 169 and 197). Persistent aphasia and isolated memory impairment suggest focal damage to the brain, and an anatomic lesion should be sought. Dementia—cognitive and memory impairment—cannot be accurately evaluated in patients who have a depressed state of consciousness or the other mental changes indicated above. When dementia occurs *de novo* in a patient with a clear sensorium, it may indicate either reversible conditions (e.g., drug-induced, depression-related) or irreversible damage (e.g., diffuse anoxia or ischemia; see Chapter 169).

Any recent change of mental status in a patient in the ICU requires *prompt* investigation. Whether it signals worsening of the underlying medical disorder or direct involvement of the brain, the change should be assessed by an experienced neurologist as early in its evolution as possible, before it is complicated by the passage of time, advance of disease, and effects of additional treatments.

Support of Respiration and Other Vital Functions

Respiratory support is needed for neurologic patients in two circumstances: loss of brainstem reflex control of respiration and impairment of effective transmission of reflex impulses to functioning respiratory muscles. Ischemia, anoxia, compression, hemorrhage, and toxic depression may alter brainstem control of respirations, producing characteristic respiratory patterns that depend on the site of damage [2], such as central neurogenic hyperventilation, Cheyne-Stokes or periodic breathing, or apnea. The intensivist and neurologist should be familiar with the use of positive end-expiratory pressure and other ventilatory regimens, operation and interpreting read-out of the hospital's respirators, and the endotracheal intubation equipment. Further, the neurologist must understand the neurologic significance of different respiratory patterns, which are as much a part of the ICU neurologic examination as is reflex testing.

Effective transmission of respiratory impulses may be impaired at the cervical spinal cord, anterior horn cells, peripheral nerves, neuromuscular junctions, or muscles of respiration. Cervical traumatic injuries, amyotrophic lateral sclerosis, Guillain-Barré syndrome, myasthenia gravis, and muscular dystrophy may interfere with breathing at the respective levels noted. Some of these conditions are transitory (e.g., Guillain-Barré syndrome) or treatable (e.g., myasthenia gravis), with complete recovery depending largely on the success of maintaining respiration. Even in incurable conditions (e.g., amyotrophic lateral sclerosis), sustaining respiration during periods of decompensation, such as respiratory infections, can prolong life significantly.

Monitoring of Intracranial Pressure and State of Consciousness

In a number of neurologic disorders, extremely close observation is needed to avoid the development of dangerous, often irreversible, further damage to the brain. The most common disorder requiring such monitoring is head trauma. The lethargic patient must be carefully observed for evidence of increasing ICP due to cerebral edema, intracranial (subdural, epidural, intracerebral) hemorrhage, or both [4].

The need for prompt recognition and early treatment of significantly increased ICP cannot be overemphasized. Once uncal or tonsillar herniation with brainstem compression and development of Duret hemorrhages has occurred, the consequences of this secondary effect of brain injury may far outweigh the initial damage. (The methods for monitoring ICP with pressure-detecting catheters or bolts and assessing

consciousness and brainstem functions with the Glasgow Coma Scale are described in Chapters 28 and 169.)

Determination of Brain Death

With the recognition that death of the brain and brainstem is equivalent to death of the patient, even though the heart continues to beat and respirations are sustained by artificial ventilation, the need to ascertain brain death has become more critical [5]. Early identification of brain death has three important justifications: (a) the use of viable donor organs for transplantation, (b) the termination of the hopeless vigil of a distraught family, and (c) the freeing of ICU beds for patients who may be helped. When one or more of these conditions prevails, it is important to determine the occurrence of brain death promptly. When none of the conditions is present, there is no urgency in declaring the patient brain dead.

It should be emphasized that brain death is specifically a determination that the brain and the brainstem are already dead—not a prediction that useful recovery is unlikely. It is also true that the longer one waits in even marginally uncertain cases, the clearer the evidence of brain death becomes. (The criteria for brain death are discussed extensively in Chapters 169 and 185.) The "CADRE" mnemonic may be useful in recalling the established criteria for brain death, in the absence of sedative drugs: *C*oma; *A*pnea; *D*ilated, fixed pupils; *R*eflex (brainstem) absence; and *E*lectroencephalographic silence.

Prevention of Further Damage to the Central Nervous System

A variety of neurologic disorders have the potential to cause further damage to the central nervous system. Acute strokes, or stroke in evolution, for example, may be arrested by thrombolytic treatment [6], endovascular clot removal or angioplasty, and stenting. These modalities may limit or even reverse the underlying ischemic process; and neuroprotective agents may, in the foreseeable future, prevent further damage. Coma following cardiac arrest should be promptly treated with hypothermia to preserve neurological function [7]. Spinal cord compression by metastatic tumor urgently requires surgical decompression followed by radiation therapy to avoid irreversible complete cord transection [8]. Among the infectious diseases of the nervous system, bacterial meningitis and certain treatable encephalitides (e.g., herpes simplex) require the immediate institution of antibiotic or antiviral therapy; spinal epidural abscess requires prompt surgical decompression as well. Although much of neurologic practice involves disorders for which progress is measured in months or years, cerebral anoxia, ischemia, hemorrhage, increased ICP, spinal cord compression, infectious diseases, and other acute disorders require prompt institution of treatment to avoid extension of the initial process. It is useful to remember that, as a largely post-mitotic structure, the brain has limited capability of regeneration, and its ability to survive without a continuing supply of nutrients is measured in minutes. Only in the ICU, with its facilities for careful monitoring and adjustment of therapy, can many of these treatments be successfully carried out.

Management of Status Epilepticus

Unlike simple, brief seizures, status epilepticus threatens lasting deficits or death if not controlled (see Chapter 172). Any patient whose sequential seizures cannot be arrested promptly with routine management (e.g., intravenous benzodiazepines, phenytoin) must be observed in the ICU, where therapy ranging up to general anesthesia with artificial ventilation may be required.

Evaluation of Neurologic Disease Accompanying Severe Medical Disease

Neurologic signs or symptoms develop in many patients admitted to the ICU for myocardial infarction, subacute bacterial endocarditis, cardiac arrhythmia, pneumonia, acute respiratory distress syndrome, septic shock, renal disease, hepatic failure, and other similar disorders while they are under treatment for the primary medical problem. Numerous questions are raised: Is the neurologic finding a consequence of the underlying disease, or is it coincidental? Does it demand further investigation at once, or can it wait? Should therapy be changed, or should new therapy be started? These issues demand the attention of the neurologist.

Management of Severe Medical Disease Accompanying Neurologic Illness

In patients with severe medical disease accompanying neurologic illness, unrelated medical illness most often develops in the setting of a chronic neurologic disorder. The demented patient may experience a myocardial infarct, or septicemia may develop in the patient with multiple sclerosis. Indirect relationships should be sought. Does the demented patient have multiple cerebral emboli from underlying cardiac disease? Is the patient with multiple sclerosis septicemic from a bladder infection due to impaired urinary control? Early recognition of a change in the seriousness of the neurologic patient's condition is often difficult, but it may be critical to a successful outcome.

PROGNOSTIC AND ETHICAL CONSIDERATIONS

When severe damage involves the brain, either as a separate neurologic condition or as a secondary consequence of other medical disease, the physician who requested neurologic consultation and the family often need guidance regarding the probable outcome. There are three critical questions: Will the patient survive? Has irreversible brain damage occurred? What is the likely degree of residual disability?

There are few simple rules that can be applied infallibly to determine the prognosis in, for example, comatose patients, especially early in the course. The most important consideration is often whether irreversible damage has affected crucial areas of the brain, rather than the depth of impairment of consciousness. The patient with glutethimide poisoning, for example, may show no evidence of any neurologic function yet can recover fully if vital functions are maintained. In contrast, the comatose patient with head trauma resulting in pontine hemorrhage and decerebrate rigidity may have a far worse prognosis. The probability of neurologic recovery generally declines with advancing age, size and location of the lesion, and duration of deficit. A number of studies have provided statistical guidelines that are of value in gauging the probability of recovery [9,10]. Guidelines for the evaluation of prognosis following cardiac arrest and resuscitation are particularly well documented, and the absence of pupillary and corneal reflexes or motor response to pain, the occurrence of myoclonic status epilepticus, absence of somatosensory evoked potentials (N20), and elevated neuron-specific enolase are particularly useful in early determination of poor prognosis (9).

Early in the course of coma, the physician should not be hasty in abandoning hope and vigorous medical efforts to maintain survival and to limit neurologic damage. Late in the course, or as poor prognostic signs accumulate, it is important to recognize the outer limits of possible recovery and to assess the value of continuing life support accordingly. The patient's wishes, expressed in a living will or durable power of attorney for health care and as interpreted by close, responsible family members ("substituted judgment"), should combine with the physician's prognostic judgment to help determine a medical course of action. Although management in the ICU usually entails the unstinting use of every available means of life support and treatment, there must eventually be a transition either to recovery or to a permanent state of dependence, and the nature and extent of continued treatment should be adjusted accordingly. The technical means of maintaining survival almost indefinitely by the use of extraordinary measures is now available. It is important for the physician and the patient's family to consider whether, in the case of a patient with irreversible and severe neurologic damage, they are extending life or prolonging the process of dying [11].

It is clear that neurologic problems abound in the ICU. A successful approach to these disorders requires the physician to recognize the nature of the clinical situation prompting neurologic consultation or admission to the ICU. An analysis of which of the nine types of neurologic clinical situations is being encountered often guides the physician initially in diagnosis and management. The following chapters discuss some of the more common neurologic problems encountered in the ICU, with specific attention to management in the ICU and a broader view of the neurologic conditions in general.

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CHAPTER 169 ■ EVALUATING THE PATIENT WITH ALTERED CONSCIOUSNESS IN THE INTENSIVE CARE UNIT

RAPHAEL A. CARANDANG, LAWRENCE J. HAYWARD AND DAVID A. DRACHMAN

The spectrum of disease that leads to acute impairment of consciousness is broad; the disorders are varied and potentially life threatening and may be treatable if recognized early. The clinician evaluating the patient with an altered level of consciousness must do so in a systematic and efficient fashion. The approach consists of (a) rapidly determining the type of mental status change, (b) administering life support measures where urgently needed, (c) obtaining a detailed history and physical examination directed at determining more precisely the cause of the nervous system disorder, (d) selecting appropriate and informative diagnostic and laboratory studies, and (e) initiating more definitive treatment based on this assessment.

As a practical matter, *consciousness* refers to a state of awareness of self and environment that depends on intact arousal and content [1,2]. Arousal is the level of attentive wakefulness and readiness to respond to relevant sensory information. Alerting stimuli activate the ascending reticular activating system (ARAS), which extends from the superior pons to the thalamus and projects to multiple cortical areas. Diminished arousal implies dysfunction of either the ARAS or both cerebral hemispheres; lesions of the brainstem sparing the ARAS (e.g., of the medulla) or of only one hemisphere do not affect wakefulness. This chapter defines altered states of consciousness and presents a systematic approach to bedside evaluation and prognostication of the comatose patient.

ALTERED STATES OF CONSCIOUSNESS

Neurologists are frequently consulted for evaluation of patients who appear unconscious, confused, or awake and alert but noncommunicative.

Patient Who Appears Unconscious

Patients who appear unconscious lie mostly motionless, usually with the eyes closed and seemingly unaware of their environment. The causes of this condition include normal sleep, depressed consciousness, psychogenic coma, locked-in state, vegetative states, minimally conscious state, and brain death.

Sleep

The normal unconsciousness of sleep is characterized by prompt reversibility on threshold sensory stimulation, and maintenance of wakefulness following arousal. The degree of stimulation required depends on the stage of sleep (stage IV non–rapid eye movement sleep is the deepest) and the sensory stimulation used.

Depressed Consciousness

Consciousness is deemed depressed when suprathreshold sensory stimulation is required for arousal and wakefulness cannot be maintained unless the stimulation is continuous [1,2]. Responsible specific lesions involve the ARAS or both cerebral hemispheres; the former by brainstem damage, or compression due to masses situated in other compartments, and the latter by multifocal insults or unilateral lesions with associated major mass effect. In addition, a wide array of metabolic derangements, toxins, or diffuse injuries may depress consciousness by affecting the ARAS, the cerebral hemispheres, or both. The spectrum of depressed states—lethargy, hypersomnolence, obtundation, stupor, and coma—is defined by the level of consciousness observed on examination. The etiologies are diverse (Table 169.1), with the degree of depression dependent on the nature of the insult, its duration, and the location and extent of the brain injury.

The first signs of brain dysfunction may be mild and barely noticeable. The patient may be described initially as confused or drowsy before progressing to *lethargy* or *hypersomnolence* and eventually to a more depressed state. Hypersomnolent patients maintain arousal only with vigorous and continuous sensory stimulation; while awake, however, they may be oriented and make appropriate responses. The most common cause of hypersomnolence in the hospital is sleep deprivation, mostly iatrogenic, especially in the around-the-clock care setting of the intensive care unit (ICU). Patients with discrete diencephalic or midbrain tegmentum lesions may also present with hypersomnolence [3,4]. Because these lesions affect the ARAS and spare the cerebral hemispheres, cognitive content is usually preserved. Rostral extension of a midline lesion may involve thalamic structures (especially the dorsomedial nuclei) and cause difficulties with the ability to store new memories. Other mesencephalic structures may be affected and cause abnormalities of pupillary function, internuclear ophthalmoplegia, and third nerve dysfunction.

Obtunded patients usually can be aroused by light stimuli but are mentally dulled and unable to maintain wakefulness. *Stuporous* patients can be aroused only with vigorous noxious stimulation. While awake, neither obtunded nor stuporous patients demonstrate a normal content of consciousness, but both may display purposeful movements, attempting to ward off painful stimuli or to remove catheters, endotracheal tubes, or intravenous lines.

Patients in *coma* are unresponsive to suprathreshold sensory stimulation, including noxious stimulation that is strong enough to arouse a deeply sleeping patient but not strong enough to cause physical injury. Although the patient usually lies motionless, movements such as stereotyped, inappropriate postures (decerebration and decortication) and spinal cord reflexes (triple flexion and Babinski responses) may occur. Whatever the etiology, the duration of coma is typically no longer than 2 to 4 weeks, after which one of the three conditions supervenes: arousal to full or partial recovery, a vegetative state, or death.

Most of the literature on prognosis of comatose patients comes from nontraumatic coma, largely anoxic–ischemic brain injury. A landmark paper by Levy, Plum, and associates from 1981 established the neurological examination – particularly brainstem reflexes including pupillary, corneal, and oculocephalic reflexes – as important predictors of poor outcome in nontraumatic coma [5]. Multiple studies followed which confirmed the importance of motor responses in addition to brainstem examination, and some diagnostic tests were established as useful in predicting outcomes; these are well summarized in the American Academy of Neurology Practice Parameter by Wijdicks et al., published in 2006 [6]. Given the life-or-death responsibility of the physician providing a prognosis, only clinical indicators or diagnostic tests that are highly specific with a near zero false–positive rate are utilized. A poor outcome is predicted by the absence of pupillary and corneal reflexes, absent or extensor motor responses, absent responses to caloric testing of the oculovestibular reflex at day 3 post-arrest, and the presence of myoclonic status epilepticus on day 1 post-arrest. The absence of N20 responses on somatosensory evoked potential (SSEP) testing, and the finding of serum neuron-specific enolase levels more than 33 µg per L on days 1 to 3 post-arrest also indicate a poor prognosis (Fig. 169.1). Prognostication must include consideration of the etiology of the disease process, the clinical examination findings, and radiological evidence of damage to the upper pons, midbrain, diencephalon, and other vital structures for arousal.

TABLE 169.1

DIFFERENTIAL DIAGNOSIS OF DEPRESSED CONSCIOUSNESS

I. Depressed consciousness with lateralizing signs of brain disease: brain tumor, cerebral hemorrhage, cerebral thrombosis, cerebral embolism, contusion, subdural or epidural hemorrhage, brain abscess, hypertensive encephalopathy
II. Depressed consciousness with signs of meningeal irritation: meningitis, subarachnoid hemorrhage, leptomeningeal carcinoma, or lymphoma
III. Depressed consciousness without lateralizing or meningeal signs: alcohol, barbiturate, or opiate intoxication: carbon monoxide poisoning, neuroleptic malignant syndrome, anoxia, hyponatremia, hypoglycemia, diabetic coma, uremia, hepatic coma, hypercapnia, nonconvulsive status epilepticus, infectious encephalitis, acute hydrocephalus, concussion, diffuse axonal injury, hypothermia

Adapted from Adams RD, Victor M: *Principles of Neurology*. 4th ed. New York, McGraw-Hill, 1989.

Psychogenic Coma

Patients in psychogenic coma appear comatose but have clinical and laboratory evidence of wakefulness [1]. Psychogenic unresponsiveness may be suggested by active resistance or rapid closure of the eyelids, pupillary constriction to visual threat, fast phase of nystagmus (i.e., a saccade) on oculovestibular or optokinetic testing, and avoidance of self-injury (e.g., by averting an arm dropped toward the patient's face) or annoying stimulation such as a nasal tickle (moving head away from stimulus). Caloric testing with ice water irrigation of the ear will elicit a

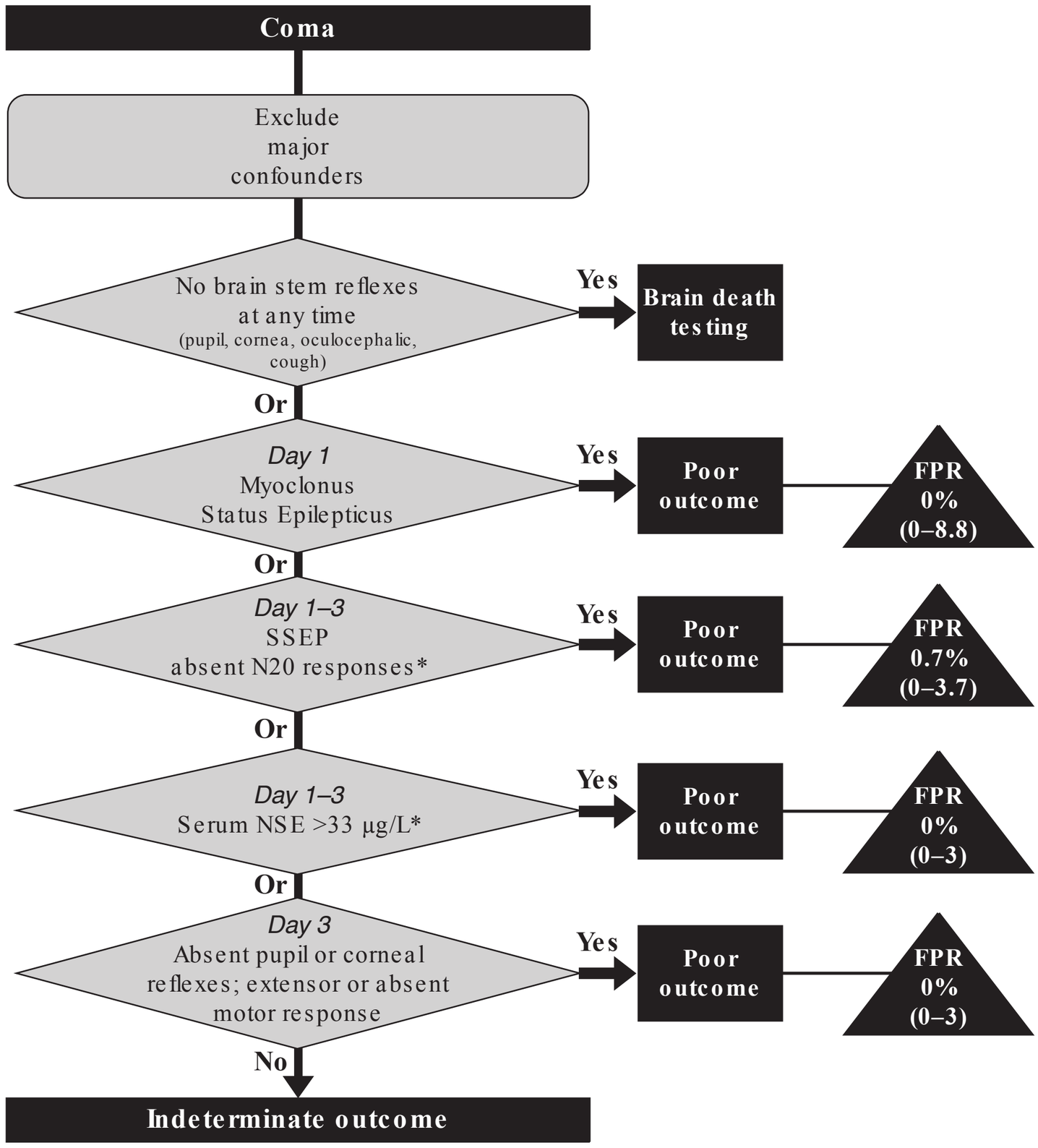

FIGURE 169.1. Algorithm for predicting outcome in comatose patients after cardiopulmonary arrest. FPR, false positive rate; NSE, neuron-specific enolase; SSEP, somatosensory evoked potential. [From Wijdicks EFM: The diagnosis of brain death. *N Engl J Med* 344:1215, 2001.]

normal nystagmoid response with the fast or corrective component directed away from the irrigated ear and possibly some nausea and vomiting. Deep tendon reflex examination is often normal but can be voluntarily suppressed. EEG alpha waves that attenuate with eye opening are inconsistent with coma or sleep. Most diagnostic tests will be unrevealing. Psychiatric conditions that may be associated with psychogenic coma are conversion reactions secondary to hysterical personality, severe depression, or acute situational reaction, catatonic schizophrenia, dissociative or fugue states, severe psychotic depression, and malingering.

Locked-in State

The locked-in state is a nearly total paralysis without loss of consciousness [7,8]. Because the most common cause of this state is destruction of the base of the pons, the patient is completely paralyzed except for muscles subserved by midbrain structures (i.e., vertical eye movements and blinking). Consciousness is preserved because the ARAS is located in the tegmentum of the pons, dorsal to the damaged area. The most frequent cause is cerebrovascular such as cerebral infarction from a basilar thromboembolism or pontine hemorrhage from uncontrolled hypertension; less frequent etiologies of the syndrome are acute polyneuropathy (Guillain-Barré syndrome), acute poliomyelitis, toxins that block transmission at the neuromuscular junction, and myasthenia gravis. It is important to note that locked-in patients are capable of hearing, seeing, and feeling external stimuli and pain. Adequate analgesia and anxiolysis should be provided despite the absence of external signs of pain and anxiety. A 5- to 10-year survival has been reported in as high as 80% of patients in some series and a surprising 58% of patients surveyed reported satisfaction with life despite their disability in a small case series [8].

Brain Death

The term *brain death* refers to a determination of physical death by brain-based, rather than cardiopulmonary-based, criteria [9]. Brain death is the irreversible destruction of the brain, with the resulting total absence of all cortical and brainstem function, although spinal cord reflexes may remain [10,11]. It is not to be confused with severe but incomplete brain damage with a poor prognosis or with a vegetative state, conditions in which some function of vital brain centers still remains. In brain death, support of other organs is futile for the patient, whereas when there is some residual brain or brainstem function, or a vegetative state, decisions regarding ongoing life support clearly depend on the wishes of the patient or his or her proxy.

In brain death, pupils are mid-position and round (not oval), and apnea persists even when arterial carbon dioxide tension (PCO_2) is raised to levels that should stimulate respiration. Table 169.2 summarizes the guidelines used in the United States. Brain death may be simulated by drug intoxications and cannot be evaluated when toxic drugs are present; depending on preserved renal and hepatic function most such toxic

TABLE 169.2

CRITERIA FOR BRAIN DEATH

Prerequisites
1. Clinical or neuroimaging evidence of an acute CNS catastrophe compatible with the clinical diagnosis of brain death
2. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid–base, or endocrine disturbance)
3. No drug intoxication or poisoning
4. Core temperature = 32°C (90°F)

1. Cerebral functions are absent.
   Coma, and absence of motor responses including decerebrate posturing, although spinal reflexes may be seen
2. Brainstem functions are absent.
   Absence of pupillary responses to light; pupils at mid-position and dilated
   Absent corneal reflexes, caloric reflexes, gag reflex, cough in response to tracheal suctioning, sucking and rooting reflexes
   Absence of respiratory drive at $PaCO_2$ 60 mm Hg, or 20 mm Hg above normal base-line values
   Interval between two separate examinations varies depending on the age of the patient if pediatric, but for adults is usually at least 6 hours
3. Ancillary Diagnostic tests:
   EEG showing electrocerebral silence
   Technetium Tc 99m hexametazime nuclear scan showing absence of activity in brain
   Cerebral angiography showing absence of blood flow in cerebral vessels
   Transcranial Doppler showing lack of diastolic or reverberating flow and small systolic peaks in early systole

Revised table from AAN Practice Guidelines. A Report of the Quality Standards Subcommittee of the American Academy of Neurology 1994; and Wijdicks EFM: The diagnosis of brain death. *N Engl J Med* 344:1215, 2001.

effects do not persist longer than 36 hours. Hypothermia also precludes a diagnosis of brain death, and the patient must be brought to normal temperature prior to declaring death. Brain death is a clinical diagnosis, but ancillary tests such as an EEG and blood flow studies (transcranial Doppler, technetium-99 m scan, or conventional cerebral angiography) may be useful where the clinical examination is compromised by sedating medications. Unresponsiveness that can mimic brain death may occur with extensive brainstem destruction, for example, after basilar artery thrombosis. Despite absent brainstem reflexes, continued cortical activity on the EEG and persistent cerebral blood flow would demonstrate that the patient is not brain dead.

The American Academy of Neurology has published practice parameters for the determination of brain death. The criteria take into account etiology, performance of two separate clinical examinations 6 hours apart, and include the method of apnea testing with preoxygenation and oxygen [11]. Since criteria for brain death vary from state to state, and procedures to determine brain death differ among institutions, it is important to be familiar with the guidelines in your institution [12]. The occurrence of brain death provides the opportunity for organ donation, and most institutions have a protocol that includes informing organ bank organizations to facilitate this.

Patient Who Appears Confused

Confusion is a general term used for patients who do not think with customary speed, clarity, or coherence. The causes of this condition include an acute confusional state, dementia, inapparent seizures, and receptive aphasia.

Acute Confusional State

When the cerebral hemispheres are insulted by toxic, metabolic, anoxic, structural, or infectious processes, the patient may appear acutely confused [13,14]. Poor arousal and an abnormal content of consciousness may contribute to the clinical presentation, and the etiologies are legion (Table 169.3). Patients with clouded consciousness are easily distracted or startled by environmental stimuli. Their processing of information is slow and effortful, arousal fluctuates from drowsiness to hyperexcitability, and poor attention span impairs recall and recent memory. If sensorial clouding becomes more advanced, sensory input is increasingly misinterpreted, daytime drowsiness alternates with nocturnal agitation, disorientation for place and time becomes apparent, and repeated prompting is required for a response to even the simplest commands.

Delirious patients typically manifest acutely fluctuating confusion, with psychomotor overactivity, agitation, autonomic instability, and often visual hallucinations. Clinical observations frequently suggest that the disturbance of cognition or perception is directly related to a potentially reversible general medical condition rather than to an evolving dementia. Hyperexcitability may alternate with periods of drowsiness or relative lucidity. Signs of autonomic overactivity include pupillary dilatation, diaphoresis, tachycardia, and hypertension. Patients with delirium may not sleep, sometimes for periods of several days; the success of treatment can be judged by the development of normal sleep. Delirium tremens, the most serious consequence of ethanol withdrawal, is perhaps the best-known example of this state. Because the routine Mini-Mental State Examination often cannot be administered to unstable, intubated patients, alternative screening tools have been developed for early detection and monitoring of delirium in the ICU [15,16]. Validated tools such as the Confusion Assessment Method, or CAM-ICU scale, have the advantage of being simple and easy to administer, highly reliable and applicable in patients who are intubated. Systematic screening may help detect early delirium and allow prompt, cost-effective treatment. Delirium has been linked to prolonged ICU stay and ventilator days, and is associated with postdischarge cognitive dysfunction and worse 6-month mortality outcomes [16,17]. The use of interventions that reduce delirium in the ICU include reduction and intermittent use of sedatives, or spontaneous awakening trials, as well as sedation with alpha adrenergic medications such as dexmedetomidine [18,19].

In beclouded dementia, confusion is superimposed on an underlying subacute or chronic cognitive disorder. The preexisting cerebral dysfunction may be mental retardation, dementia, or the deficits from a vascular, neoplastic, or demyelinative process. In some cases, the underlying disorder is not diagnosed until the confusion appears during an intercurrent illness (e.g., sepsis or infection, congestive heart failure, surgical procedures, anemia, drug overdose, or intolerance).

Dementia

Patients with dementia have subacute or chronic intellectual dysfunction unaccompanied by a reduction in arousal [20]. The patient exhibits a decline in multiple cognitive functions, including memory, language, spatial orientation, personality, abstract thinking, and insight. The ability to carry out testing requires relative preservation of attention and language

TABLE 169.3

CLASSIFICATION OF ACUTE CONFUSIONAL STATES

ACS not associated with focal or lateralizing neurologic signs and normal CSF
- Metabolic disorders
  - Hepatic encephalopathy
  - Uremia
  - Hypercapnia
  - Hypoglycemia
  - Diabetic ketotic coma
  - Porphyria
  - Hypercalcemia
- Infectious disorders
  - Septicemia[a]
  - Pneumonia[a]
  - Typhoid fever[a]
  - Rheumatic fever[a]
- Drug intoxication
  - Opiates
  - Barbiturates
  - Tricyclic antidepressants
  - Other sedatives
  - Amphetamines[a]
  - Anticholinergic medications[a]
- Abstinence states (i.e., withdrawal states)
  - Alcohol (delirium tremens)[a]
  - Barbiturates[a]
  - Benzodiazepines[a]
- States that reduce cerebral blood flow or oxygen content
  - Hypoxic encephalopathy
  - Congestive heart failure
  - Cardiac arrhythmias
- Situational psychoses (diagnoses)
  - Postoperative psychosis[a]
  - Posttraumatic psychosis[a]
  - Puerperal psychosis[a]
  - Intensive care unit psychosis[a]

ACS associated with focal or lateralizing neurologic signs and/or abnormal CSF
- Cerebrovascular disease or space-occupying lesions (especially of the right parietal, inferofrontal, and temporal lobes)
  - Ischemic infarct[a]
  - Neoplasm[a]
  - Abscess[a]
  - Hemorrhage (intraparenchymal, subdural, epidural)[a]
  - Granuloma
- Infectious disorders
  - Meningitis[a]
  - Encephalitis[a]
- Subarachnoid hemorrhage[a]
- Cerebral contusion and laceration[a]

ACS sometimes associated with focal or lateralizing neurologic signs
- Postconvulsive delirium[a]
- Acute hydrocephalus
- Nonconvulsive status epilepticus
- Nonketotic diabetic coma

[a]These disorders may be associated with signs of psychomotor overactivity or delirium.
ACS, acute confusional state; CSF, cerebrospinal fluid.
Adapted from Adams RD, Victor M: *Principles of Neurology*. 4th ed. New York, McGraw-Hill, 1989.

comprehension. The causes of dementia include degenerative processes (Alzheimer's disease, Pick's disease, Huntington's disease), metabolic and nutritional disorders (hypothyroidism, pellagra, vitamin B_{12} deficiency), infectious diseases (subacute spongiform encephalopathy, acquired immunodeficiency syndrome dementia, neurosyphilis, chronic meningitis, progressive multifocal leukoencephalopathy), cerebrovascular disorders (multi-infarct dementia, anoxia-ischemia), hydrocephalus with normal or increased intracranial pressure, and toxins.

Inapparent Seizures

Patients with nonconvulsive status epilepticus may appear disoriented, episodically unresponsive, or alternately lucid and confused; the EEG shows continuous or frequent epileptiform discharges [21,22]. Careful observation may alert the clinician to seizure phenomena, such as episodic staring, eye deviation or nystagmoid jerks, facial or hand clonic activity, and automatisms. The syndrome may be the result of a generalized (absence) status or a complex partial status. Complex partial status is the more common form seen in the ICU and may not be preceded by a history of complex partial seizures. The origin of the abnormal focal discharge may be from the temporal, frontal, or occipital lobes, and the EEG pattern during the ictus is variable. Inapparent seizures may occur in as many as 19% of all patients in the ICU, and 56% of patients who are comatose at the time of the monitoring. The yield of EEG monitoring is increased by continuous monitoring for 24 hours [23]. Nonconvulsive status epilepticus should be considered, and is the cause of otherwise unexplained coma in as many as 8% of patients [24]. A benzodiazepine, such as diazepam or lorazepam, may eliminate the discharge and improve the patient's confusion.

Receptive Aphasia

Patients with receptive aphasia often appear confused because they have a disorder of language comprehension [14]. The patient is awake and alert but unable to comprehend written or verbal commands despite voluminous (fluent) spontaneous speech. Paraphasias may be present (especially when the patient is asked to name objects) and consist of either inappropriately substituted words or nonsensical jargon. The responsible lesions are located in the dominant temporoparietal cortex and are often associated with subtle focal neurologic signs, including mild pronator drift of the right hand, right homonymous hemianopsia or superior quadrantanopsia, and right-sided sensory loss; gross hemiparesis is usually not found, as the frontal motor cortex is not affected.

Patient Who Appears Awake and Alert but Noncommunicative

Although sensory stimulation may arouse these patients, they seem unable or unwilling to speak. The causes of this condition include mutism, akinetic mutism, and the persistent vegetative state.

Mutism

Mutism is a manifestation of many clinical conditions, including aphonia, anarthria, oral-lingual apraxia, and aphasia. Only in aphasia, however, is written expression also impaired (i.e., agraphia).

Aphonia due to paralysis of the vocal cords and anarthria due to paralysis of the articulatory muscles are usually evident clinically in patients who are unable to make sounds but who mouth words appropriately. Oral-lingual (facial) apraxia is a disorder of learned mouth movements (e.g., speaking,

blowing kisses, sucking through a straw, protruding the tongue to command) seen with isolated and discrete lesions involving the facial area of the dominant motor cortex [14,25].

Patients with expressive aphasia are unable to communicate normally by verbal or written language [1,13,14]. Nonfluent (Broca's) aphasia with diminished "telegraphic" output is usually intensely frustrating to the patient; occasionally, singing his or her words, rather than merely saying them, improves speech. Lesion location differs depending on whether comprehension is also affected or whether comprehension and repetition of words are relatively preserved or lost. At the least, the dominant frontal cortex is involved, and some degree of right hemiparesis is usually present.

Akinetic Mutism

Patients with akinetic mutism appear alert and exhibit sleep–wake cycles, but they show little evidence of cognitive function and do not meaningfully interact with the environment [1,14]. Brainstem function is intact, and patients may open their eyes to verbal stimuli or track moving objects. They have a paucity of movement even to noxious stimulation, despite little evidence of corticospinal or corticobulbar damage. Akinetic mutism is associated with large bilateral lesions of the basomedial frontal lobes, small lesions of the paramedian reticular formation in the posterior diencephalon and midbrain, and subacute communicating hydrocephalus.

Persistent Vegetative State

Patients in a persistent vegetative state are also akinetic and mute but lack outward manifestations of any significant brain activity other than reflex responses [1,14]. These may include decerebrate or decorticate posturing, deep tendon reflexes, Babinski or triple flexion reflexes, yawning, and so on. The term is usually reserved for the patient who has recovered only to this extent from coma due to a severe anoxic, metabolic, or traumatic brain injury, and has been in this condition for over a month. Neuropathologic findings in anoxic encephalopathy may include cortical pseudolaminar necrosis, cerebellar Purkinje cell loss, and necrosis of hippocampal cortex but relative sparing of brainstem structures [26]. Persistent vegetative state is considered permanent if the patient has been in this state for 3 months after nontraumatic or anoxic brain injury, and more than 12 months after traumatic brain injury [27].

Minimally Conscious State

These are patients who, similar to those in the vegetative state, have severely impaired consciousness, also manifest the posturing, reflexes, and diurnal cycles, but in addition show evidence of self and environmental awareness. They may follow simple commands, give gestural yes or no responses, verbalize intelligibly, and do other purposeful behaviors and visual tracking [1,13,14]. This is considered to be a transitional phase of recovery from coma after PVS, and patients with traumatic brain injury who are in a minimally conscious state have significantly better outcomes at 1 year than PVS patients. Many publicized reports of late recoveries from vegetative states were actually patients in MCS.

BEDSIDE EVALUATION OF THE COMATOSE PATIENT

Coma in the ICU is a medical emergency. The goal of each evaluation is to identify and treat promptly (if applicable) the cause of the comatose state; even if no definitive treatment is available, general medical and neurologic support is necessary. A neurologic consultation should be obtained early; the practice of obtaining imaging studies before a careful and systematic examination is often counterproductive when it delays focused evaluation and treatment. The proper approach requires (a) immediate administration of life-support measures, (b) completion of a general physical examination, (c) performance and interpretation of the neurologic examination, (d) selection of ancillary tests, and (e) institution of definitive treatment, based on the above observations.

Initial Measures

As in all emergencies, vital signs, respiration, and circulation are first stabilized and monitored; the comatose patient often requires an endotracheal tube for respiratory support and airway protection. A large-bore intravenous line is started, and the blood is drawn for a complete blood cell count, glucose, electrolytes (including Ca^{2+}), blood urea nitrogen, creatinine, liver transaminases, and a toxicology screen. Arterial blood is obtained for determination of oxygen tension, PCO_2, and pH. If there is any doubt about the etiology of coma, 100 mg thiamine, 50 g glucose, and 0.4 mg naloxone are administered intravenously.

General Physical Examination

In addition to the usual complete examination, several points warrant special attention [1,2,13]. Severe hypothermia (rectal temperature less than or equal to 32°C or 89.6°F) may cause coma (as in elderly patients exposed to the cold) or provide clues to other etiologies (e.g., overwhelming sepsis, drug or alcohol intoxication, hypothyroidism, hypoglycemia, Wernicke's encephalopathy) [28]. Severe hyperthermia may result from intracranial causes, including infection and anterior hypothalamic or pontine destruction. Meningeal signs (e.g., nuchal rigidity) may be absent in deeply comatose patients, even in the presence of overwhelming bacterial meningitis. This sign should never be sought if cervical spine fracture or dislocation is suspected.

The skin should be thoroughly inspected for signs of trauma. Basilar skull fractures may be signaled by blood behind the ear (Battle's sign), cerebrospinal fluid rhinorrhea, or otorrhea. Orbital fractures may cause bleeding into periorbital tissues ("raccoon eyes").

The breath odor may suggest metabolic derangement or intoxication. The spoiled fruit odor of diabetic coma, the uriniferous odor of uremia, and the musty fetor of hepatic encephalopathy sometimes can be recognized. Although the odor of alcohol is usually noted, its presence does not rule out superimposed structural causes of coma (e.g., subdural hematoma), and its absence does not rule out intoxication with odorless spirits (e.g., vodka).

Respiratory patterns in comatose patients are distinctive [1,13,14]. Bilateral hemispheric or diencephalic disturbances as well as systemic disorders may lead to periodic breathing in which increasing and then decreasing breaths (crescendo–decrescendo) alternate with apnea (Cheyne-Stokes respirations). Lesions of the midbrain-pontine tegmentum may give rise to tachypnea and a respiratory alkalosis unresponsive to oxygen (central neurogenic hyperventilation), but this is much less common than hyperpnea due to low oxygen tension, metabolic acidosis, or a primary respiratory alkalosis (e.g., salicylate poisoning). Lesions of the inferior pons may be associated with 2- to 3-second pauses following full inspiration (apneustic breathing). Compressive or intrinsic lesions of the medulla may cause chaotic breathing of varying rate and depth (Biot's breathing). Complete brainstem destruction results in apnea that is unresponsive to elevated PCO_2.

Neurologic Examination

The goal of the neurologic examination in the comatose patient is to determine the location of the lesion (ARAS or bilateral cerebral hemispheres) and its etiology (structural, causing destruction or compression of brain substance; toxic, metabolic, anoxic, or traumatic, affecting the nervous system in a diffuse or multifocal manner; subarachnoid blood or infection; or nonconvulsive status epilepticus). A critical part of this determination is the medical history, and heroic efforts to locate family members, witnesses, and medication lists are almost always rewarded. For example, truly sudden coma in a healthy person suggests drug intoxication, intracranial hemorrhage, meningoencephalitis, or an unwitnessed seizure.

Often an intubated patient with altered mental status will be on pharmacological sedation or anxiolysis for management of respiration, or safety in agitated or combative patients. Neurological examination should be performed after discontinuing any sedating medication that may alter the patient's responsiveness and significantly alter the examination findings.

Neurologic assessment must include a description of the level of consciousness, examination of the pupils, direct ophthalmoscopy, observation of spontaneous and induced ocular movements, elicitation of the corneal reflex, and tests of motor system function (including spontaneous and induced limb movements and asymmetries of tone), deep tendon reflexes, pathologic reflexes, and response to sensory stimulation—often pain. The importance of repeat examinations to document the temporal course of the patient's condition cannot be overemphasized.

Level of Consciousness

The level of consciousness is determined first by observing the patient undisturbed for several minutes. Any spontaneous (e.g., yawning, sneezing) or responsive (e.g., to ventilator noise) movements or postures are noted. A battery of graduated sensory stimuli is applied (whispered names, shouted names, loud noise, visual threat, noxious stimulation by supraorbital compression, vibrissal (nasal) stimulation, sternal rub, nail bed compression, or medial thigh pinch) and the response recorded (e.g., opens eyes, squeezes eyes shut, blinks symmetrically to visual threat, nods, turns head, groans, grimaces, purposefully withdraws, displays stereotyped posturing). Such careful documentation allows serial assessments of subtle changes over time by multiple examiners.

Serial documentation and accurate and reliable communication of findings can be facilitated by the use of standardized scales such as the Glasgow coma scale. While originally intended for use in traumatic brain injury, the Glasgow coma scale has become widely used and has been found to be predictive of outcomes, particularly in traumatic brain injury (Table 169.4). Because of its limitations, a more comprehensive coma scale called the Full Outline of Unresponsiveness, or FOUR score, incorporates brainstem reflexes and respiration [1,13,14,29]. These grading scales are helpful to standardize assessment, improve communication and serial monitoring, but are limited and cannot be substituted for a detailed bedside neurological examination.

Pupils

The pupils are examined for size, equality, and reactivity to light. Normal pupils confirm the integrity of a circuit involving the retina, optic nerve, midbrain, third cranial nerve, and pupillary constrictors. A strong flashlight and magnifying glass, or an ophthalmoscope, are usually necessary, and darkening the room is helpful.

TABLE 169.4

COMA GRADING SCALES

Glasgow Coma Scale

Eye response
- 4 = eyes open spontaneously
- 3 = eye opening to verbal command
- 2 = eye opening to pain
- 1 = no eye opening

Motor response
- 6 = obeys commands
- 5 = localizing pain
- 4 = withdrawal from pain
- 3 = flexion response
- 2 = extension response
- 1 = no motor response

Verbal response
- 5 = oriented
- 4 = confused
- 3 = inappropriate words
- 2 = incomprehensible words
- 1 = no verbal response

FOUR score

Eye response
- 4 = eyelids open or opened, tracking, or blinking to command
- 3 = eyelids open but not tracking
- 2 = eyelids closed but open to loud voice
- 1 = eyelids closed but open to pain
- 0 = eyelids remained closed with pain

Motor response
- 4 = thumbs up, fist or peace sign
- 3 = localizing to pain
- 2 = flexion response to pain
- 1 = extension response to pain
- 0 = no response to pain or generalized myoclonus

Brainstem reflexes
- 4 = pupils and corneals intact
- 3 = one pupil wide and fixed
- 2 = pupil or corneal absent
- 1 = pupil and corneal absent
- 0 = absent pupil, corneal and cough reflex

Respiration
- 4 = not intubated, regular breathing pattern
- 3 = not intubated, Cheyne-Stokes breathing
- 2 = not intubated, irregular breathing
- 1 = breathes above ventilator rate
- 0 = breathes at ventilator rate or apnea

Symmetrically small, light-reactive pupils (miosis) are normally seen in elderly and sleeping patients. Opiates, organophosphates, pilocarpine, phenothiazines, and barbiturates produce small pupils that may appear to be unreactive to light, whereas a large lesion of the pons (i.e., hemorrhage) characteristically produces tiny pinpoint pupils. Symmetrically large pupils (mydriasis) that do not react to light suggest midbrain damage, but they may also be seen following resuscitation when atropine has been used (in this case, the pupils do not constrict to 1% pilocarpine) [30], in cases of anoxia, following pressor doses of dopamine [31], and often in amphetamine or cocaine intoxication. Bilaterally fixed and midposition pupils indicate absent midbrain function, although severe hypothermia [28], hypotension, or intoxication with succinylcholine [32] or glutethimide [33] must be ruled out.

Pupillary asymmetry (anisocoria) suggests neurologic dysfunction if it is of recent onset, the inequality is more than

1 mm, and the degree of anisocoria changes with ambient lighting [34]. When the larger pupil is sluggishly reactive or fixed to light (but the contralateral consensual response is spared), uncal herniation due to an ipsilateral hemispheric mass compressing the third cranial nerve against the petroclinoid ligament must be considered. Unilateral pupillary dilatation may also indicate a mass in the cavernous sinus, aneurysm of the posterior communicating artery, focal seizure, or topical atropine-like drugs (e.g., used for ophthalmoscopic examination). On the other hand, with Horner's syndrome the affected pupil is smaller. In this condition, the pupillary asymmetry is increased in darkness and the smaller pupil is associated with partial ptosis of the upper eyelid, straightening of the lower eyelid, and facial anhidrosis. It may be caused by damage to descending sympathetic fibers anywhere from the hypothalamus to the upper thoracic cord, or to ascending sympathetic fibers in the cervical sympathetic chain, the superior cervical ganglion, the carotid artery, or the cavernous sinus.

Direct Ophthalmoscopy

Direct ophthalmoscopy may be limited by miosis or cataracts, but the pupils should never be pharmacologically dilated without clear documentation (with a large sign taped to the patient's bed), or if the patient's condition is uncertain or unstable. Obscuration of the disk margins, absent venous pulsations, and flame-shaped hemorrhages suggest early papilledema from an intracranial mass or systemic hypertension [35]. Subhyaloid and vitreous hemorrhages may be observed in the patient with subarachnoid hemorrhage or suddenly increased intracranial pressure.

Ocular Movements

Assessment of ocular movements begins by observing for tonic deviation of the eyes at rest [1]. The eyes may deviate toward the side of a lesion in the motor cortex (a gaze preference—away from the hemiparetic limbs) but usually can be induced to cross the midline. The eyes deviate away from the side of a pontine lesion (toward the hemiparetic limbs) and cannot be moved across the midline (a gaze paralysis). A seizure focus in the frontal (area 8) or supplementary motor (area 6) cortex can drive the eyes or cause nystagmoid jerks contralaterally (toward the side of the convulsing limbs) [36]. Tonic upward eye deviation may be seen after anoxia [37], and tonic downward deviation may be seen in thalamic hemorrhage, midbrain compression, and hepatic encephalopathy.

Spontaneous eye movements may have a localizing value. Roving eye movements (slow and random, usually conjugate and horizontal) and periodic alternating ("Ping-Pong") gaze (cyclic, conjugate excursions to the extremes of lateral gaze every 2 to 3 seconds) [38] are found in patients with intact brainstem function. Ocular bobbing consists of a rapid conjugate downward jerk followed by a slow upward drift (rate and rhythm are variable) and suggests a lesion in the posterior fossa, especially if horizontal eye movements are impaired [39]. The reverse movement, ocular dipping (slow downward, fast upward) can be seen after anoxia and in status epilepticus [40]. Conjugate spasmodic eye movements, rotating the eyes upward for minutes or longer (oculogyric crisis), in some patients may be an untoward effect of neuroleptic medications.

If spontaneous eye movements are absent or restricted to a particular direction, reflex movements should be tested by oculocephalic ("doll's eyes") and oculovestibular (caloric) stimulation [1,17,18,41]. Full eye movements induced by these maneuvers confirm the integrity of the brainstem tegmentum from the medullary-pontine junction to the midbrain. Oculocephalic testing is never done in patients with suspected cervical spine fracture or dislocation. The maneuver is performed by holding the patient's eyelids open and briskly rotating the head from one side to the other (for horizontal eye movements) and from flexion to extension (for vertical eye movements). In comatose patients with an intact brainstem, the eyes deviate to the side opposite the direction of head movement. If the oculocephalic response is not obtained or the movements are limited or asymmetric, the oculovestibular reflex should be tested. This is never done until the tympanic membrane is examined and seen to be intact. The patient's head is elevated to 30 degrees above horizontal, and up to 120 mL ice water is instilled slowly in the external auditory meatus with a large syringe and attached Teflon catheter. Each ear is tested separately for horizontal eye movements, with a 5-minute interval between right and left ears. In awake patients (or those in psychogenic coma), nystagmus with the fast phase away from the irrigated ear is induced. In comatose patients with an intact brainstem, a tonic conjugate eye deviation toward the irrigated ear is seen; a defective response implies brainstem damage. Vertical eye movements can be induced by irrigating both ears simultaneously with cold water (eyes deviate downward) and with warm (44°C) water (eyes deviate upward). Absent or deranged responses can be caused, in addition to various brainstem lesions, by previous vestibular (labyrinthine end-organ) lesions, vestibulosuppressant drugs (e.g., benzodiazepines, antihistamines, anticholinergics), hepatic encephalopathy, and neuromuscular blockers (e.g., succinylcholine). An ophthalmoplegia after intravenous phenytoin is well known [42].

Corneal Reflex

The corneal reflex is obtained by lightly touching the limbus of the cornea with a fine material (wisp of cotton, rolled corner of tissue paper, or a squirt of saline). Both eyes should blink to unilateral stimulation, confirming the integrity of a circuit involving the fifth cranial nerve, trigeminal sensory and facial motor nuclei in the pons, and both seventh cranial nerves. A blunted corneal response is commonly seen in chronic contact lens wearers. An absent blink on the stimulated side with an intact contralateral (consensual) response indicates ipsilateral motor damage.

Motor System

The examination of the motor system identifies whether limb movements are appropriate and purposeful or inappropriate and stereotyped. Left–right asymmetries or worsening of the motor response over time must be carefully noted. Appropriate movements include spontaneous turning in bed, drawing up the sheets, crossing the legs modestly, or rapid withdrawal (especially abduction) from noxious stimulation. Inappropriate movements include spontaneous or induced flexion–internal rotation of the arms with extension of the legs (decorticate posturing) or extension-adduction of all limbs (decerebrate posturing); whether flexor or extensor postures are induced depends partly on the position of the limbs [43]. These responses may occur occasionally in toxic-metabolic coma [44,45] but are more common with anatomic brainstem lesions. Facial grimaces or groans despite absent motor responses suggest that sensory pathways are grossly intact. Flexion of the leg at the hip, knee, and ankle (triple flexion response) is a spinally mediated exaggerated Babinski reflex that may persist in brain death.

Other spontaneous movements of the limbs and trunk have been observed in brain dead patients and are all forms of spinal reflexes, including myokymia, trunk flexion and the Lazarus sign, wherein the patient actually extends and pronates his or her arms forward and then crosses them over the chest [1,17,18,46]. These signs are easily misinterpreted by family members as well as medical practitioners who are not versed in the neurological examination.

INTERPRETATION OF THE NEUROLOGIC EXAMINATION

In general, focal neurologic signs suggest a structural cause of coma. Nevertheless, focal weakness is not unknown in hypoglycemia, hyperglycemia, hyponatremia, hyperkalemia, and rarely hepatic and uremic encephalopathies [47,48]; and continuous focal motor seizures (epilepsia partialis continua) may be a presenting sign of the hyperglycemic nonketotic hyperosmolar state [49]. Focal signs due to preexisting deficits may deceive even the ablest clinician. For example, if generalized seizures from a new metabolic imbalance develop in a patient with an old hemiplegia due to a cerebral infarction, apparently focal convulsions of the nonplegic limbs might falsely suggest a structural lesion of the intact cerebral hemisphere contralateral to the previously infarcted one. Other false localizing signs include sixth nerve palsies (due to transmitted increased intracranial pressure), visual field cuts (due to compression of the posterior cerebral artery), and hemiparesis ipsilateral to a third nerve palsy (due to compression of the contralateral cerebral peduncle against the tentorium [Kernohan's notch]).

Conversely, a nonfocal examination does not invariably indicate toxic-metabolic coma. Symmetric neurologic dysfunction may be caused by meningoencephalitis, subarachnoid hemorrhage, bilateral subdural hematomas, or thrombosis of the superior sagittal sinus. Multifocal seizures, myoclonus, asterixis, or fluctuation of the examination suggests a toxic or metabolic etiology, although periodic increases in intracranial pressure (plateau waves) and nonconvulsive seizures may lead to a waxing and waning mental status.

A preserved pupillary light reflex even in deep coma with absent oculovestibular and motor responses suggests a toxic or metabolic etiology. It is important to note that the pupils may be unreactive to light in severe hypothermia, deep barbiturate coma (the patient is usually apneic and hypotensive if the pupils are fixed), and glutethimide overdose. In addition, an expanding posterior fossa mass (e.g., cerebellar hemorrhage) may present with early signs of pontine compression and small, light-reactive pupils [50].

A useful rule is that toxic-metabolic coma usually has incomplete but symmetric dysfunction of neural systems affecting many levels of the neuraxis simultaneously while retaining the integrity of other functions at the same levels. Structural coma is characterized by regionally restricted anatomic defects [1,13,14]. For example, toxic-metabolic coma might present with intact pupillary reactivity and corneal reflexes but an absence of horizontal (pontine) and vertical (midbrain) reflex eye movements to oculovestibular testing. Such a presentation would be inconsistent with coma from a structural cause.

ANCILLARY TESTS

A computed tomographic (CT) scan without contrast infusion can reliably demonstrate intracranial bleeding such as intraparenchymal, epidural or subdural hematoma, or intraventricular hemorrhage. CT scans reveal hydrocephalus and may show anoxic–ischemic brain injury, with loss of grey–white differentiation, border-zone infarction from hypoperfusion, and diffuse cerebral edema (Fig. 169.2). Other coma-inducing lesions shown by CT scan include massive middle cerebral infarction, uncal herniation, and midline shift from large mass lesions with cerebral edema. Contrast enhancement may be required for suspected infectious or neoplastic masses. The CT scan does not reliably rule out inflammation, infection, subarachnoid blood, or early ischemia. CT angiography can be helpful in showing large vessel occlusion or dissection but has limited sensitivity and specificity. A CT scan can be considered the initial brain imaging study in patients with coma if lesions that require emergent surgical intervention, such as acute cerebellar hemorrhage, are considered [1,13,14].

Magnetic resonance imaging or MRI is clearly superior to CT scan in resolution, and special sequences are highly sensitive to acute ischemia and encephalitis. MRI is superior for anatomical detail and can produce excellent images of the posterior fossa, brainstem, and craniocervical junction. Diffusion weighted MRI studies, and particularly whole brain median apparent diffusion coefficient (ADC) imaging, is useful in assessing prognosis following anoxic/ischemic coma [51,52]. While it is not always logistically possible to perform MRI imaging on patients in the ICU, whenever possible it provides important information.

The cerebrospinal fluid must be examined if meningoencephalitis is suspected or if subarachnoid blood is not visualized on the CT scan. Occasionally, a sterile cerebrospinal fluid

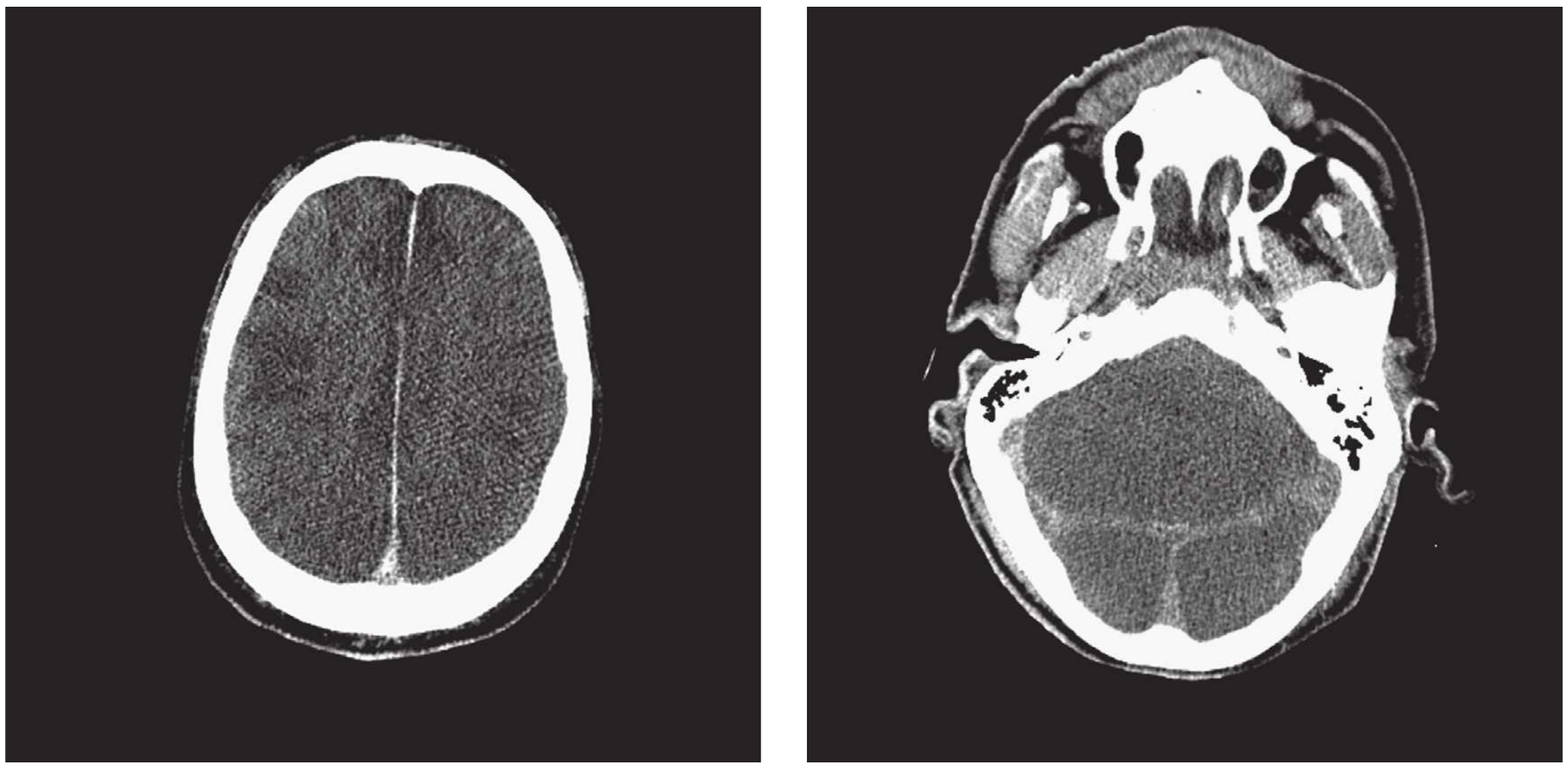

FIGURE 169.2. Noncontrast CT scan of patient with anoxic brain injury. Diffuse cerebral edema with loss of grey–white differentiation, obliteration of basal cisterns, multiple areas of hypodensity suggestive of anoxic–ischemic injury, and venous stasis with hyperdensity of the venous sinuses. This patient was brain dead clinically and by apnea testing.

pleocytosis follows status epilepticus [53]. The cerebrospinal fluid sent for protein 14–3-3 may also be useful for the diagnosis of Creutzfeldt-Jakob disease (CJD). Cytology and vascular endothelial growth factor (VEGF) levels can confirm the diagnosis of carcinomatous meningitis; and antibodies can be evaluated in paraneoplastic syndromes such as limbic encephalitis.

EEG provides a physiologic marker of brain function and may be helpful in nonconvulsive status epilepticus and psychogenic coma, and for documenting (but not primarily establishing) brain death by the presence of electrocerebral silence. In unresponsive patients, somatosensory or brainstem auditory evoked potentials may be very useful in evaluating the integrity of spinal, brainstem, or cortical pathways and, compared to EEG, are much less susceptible to drug effects and hypothermia. SSEPs are useful in prognostication of recovery from anoxic/ischemic coma during the first few days after cardiac arrest.

INITIATION OF EMERGENCY TREATMENT

Definitive treatment of altered consciousness depends on the underlying pathophysiologic process, but urgent therapeutic interventions may be required in life-threatening conditions or to prevent further central nervous system insult. Meticulous nursing care (fluid replacement, oxygenation and prevention of aspiration, nutrition, corneal protection, and conscientious skin, bowel, and bladder care) is essential. *Unnecessary sedation should be avoided*—it obscures evaluation of the patient's state of consciousness and makes assessment of any changes in the sensorium or cognition inaccessible to testing.

Recent and ongoing clinical trials are continuing to validate acute therapies that may protect the brain after insults such as cardiac arrest, traumatic brain injury, and stroke. For example, the induction of mild hypothermia (33°C for 12 to 24 hours) in comatose survivors of cardiac arrest improved the neurologic outcome in two randomized clinical trials [54,55]. Based on these studies, the American Heart Association and the International Liaison Committee on Resuscitation advised therapeutic mild hypothermia for unconscious victims of cardiac arrest [56]. Hypothermia appeared ineffective as an acute treatment for traumatic brain injury in one large randomized controlled trial [57] but may have been related to the delay in achieving goal temperature, duration of cooling, as well as other factors. A recent systematic review of 12 Randomized Controlled Trials that pooled 1,069 patients concluded that clinical mortality and outcome benefit may be derived from cooling patients with traumatic brain injury to a temperature of 32°C to 33°C for 48 hours and slowly rewarming them 24 hours after discontinuation of therapy [58]. A multicenter randomized clinical trial of early induced hypothermia for severe traumatic brain injury for 48 hours failed to show benefit but was terminated prematurely and was confounded by intracranial hypertension during rewarming [59]. There is a suggestion that hypothermia may benefit patients with acute stroke or refractory elevated intracranial pressure, but larger clinical trials are needed. Although prolonged or moderate hypothermia (28°C to 32°C) can be associated with complications of cardiac arrhythmia, coagulopathy, or infection, brief mild hypothermia appears relatively safe and effective [60,61]. If patients sustaining a neurologic insult are hypothermic upon admission to the ICU, it may be prudent to avoid aggressively warming them to normothermic levels. The benefit from mild hypothermia likely involves more complex biochemical mechanisms distinct from a simple reduction of oxygenation requirements. The deleterious effects of fever in brain injury are well documented in the laboratory and clinical outcome studies in a variety of diseases [62]. No large studies have prospectively addressed the effects of induced normothermia on outcomes. Comparison of endovascular and standard normothermia protocols to achieve a temperature of 36.5°C found no increase of adverse events, but was underpowered to show any benefit on neurologic outcome [63]. Further study in a larger sample of patients is warranted, and the development of protocols to control fever or induce normothermia is expected to benefit these patients.

CONCLUSION

Altered consciousness is common in patients in the ICU. A systematic and efficient approach is required to determine the location of the responsible lesion(s) or the cause(s) of impaired consciousness, both to allow institution of definitive therapies and to assess the prognosis accurately.

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CHAPTER 170 ■ METABOLIC ENCEPHALOPATHY

PAULA D. RAVIN

Metabolic encephalopathy is a general term used to describe any process that affects global cortical function by altering the biochemical function of the brain. It is the most common cause of altered mental status in the intensive care unit (ICU) setting, either medical or surgical, and is also one of the most treatable. Early recognition of metabolic encephalopathy, therefore, is critical to the management of the ICU patient. The patients who are most at risk for development of a metabolic encephalopathy are those with single or multiple organ failure, the elderly (> 60 years of age), those receiving multiple drugs with central nervous system (CNS) toxicity, and those with severe nutritional deficiencies such as cancer patients and alcoholics. Other risk factors include infection, temperature dysregulation (hypothermia or fever), chronic degenerative neurologic or psychiatric diseases such as dementia or schizophrenia, and endocrine disorders. Metabolic encephalopathy is always suspected when there is an altered cognitive status in the absence of focal neurologic signs or an obvious anatomic lesion such as an acute cerebrovascular accident or head injury. A patient may progress over days from intermittent agitation into depressed consciousness or quickly into coma without any antecedent signs (e.g., with hypoglycemia). In mild cases, it is easily mistaken for fatigue or psychogenic depression, whereas more severe cases may develop into coma and are life-threatening.

The altered mental status observed can start as mild confusion with intermittent disorientation to person, time, or place and difficulty attending to questions or tasks at hand. Delirium is a further change toward heightened arousal alternating with somnolence, often worse at night and fluctuating throughout the day. Finally, progression to lethargy, a state of sleepiness in which the person is difficult to arouse by vigorous stimulation, can lead into stupor or coma as impaired consciousness ensues.

TABLE 170.1

PATIENT PROFILE IN METABOLIC ENCEPHALOPATHY

Gradual onset over hours
Progressive if untreated
Waxing and waning level of consciousness
Patient treated with multiple CNS-acting drugs
Patient with organ failure, postoperative state, electrolyte disturbance, endocrine disease
No evidence of brain tumor or stroke on neurologic examination—usually nonfocal (except hypoglycemia)
Sometimes heralded by seizures—focal or generalized
Increased spontaneous motor activity—restlessness, asterixis, myoclonus, tremors, rigidity, and so forth
Abnormal blood chemistries, blood gases, anemia
Usually normal CNS imaging studies
Generalized electroencephalographic abnormalities—slowing, triphasic waves
Gradual recovery once treatment is initiated

CNS, central nervous system.

This sequence of events is often punctuated by focal or generalized tonic-clonic seizures and postictal somnolence as part of the overall clinical picture (Table 170.1).

Disorders that can be confused with metabolic encephalopathy include brain tumors, encephalitis, meningitis, closed head trauma, and brainstem cerebrovascular events. Brain tumors are usually recognizable because they produce focal neurologic deficits such as hemiplegia or hemianopsia, as do traumatic lesions of the brain and cortical strokes. Hypoglycemia can also present focally and is discussed further in the section on Hypoglycemic Encephalopathy. Brainstem stroke due to thrombosis of the basilar artery can be deceptive because there may be a gradual progression of signs and symptoms over several hours rather than a sudden presentation. Table 170.2 outlines some of the cardinal differences between brainstem stroke and metabolic encephalopathy.

EVALUATION

Clinical Examination

Initial observation of the patient's level of arousal, posture in bed, breathing pattern, vital signs, and behavioral fluctuations is highly suggestive of a metabolic disturbance in many cases. Waxing and waning levels of activity are the hallmark of metabolic encephalopathy and may occur over hours to days.

TABLE 170.3

EVALUATION FOR METABOLIC ENCEPHALOPATHY

Neurologic examination
Mental status
Pupillary responses
Oculomotor responses
Respiratory pattern
Motor activity, strength
Deep tendon reflexes, plantar responses
Initial laboratory tests
Blood sugar, electrolytes, lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, ammonia, blood urea nitrogen, creatinine, white blood cell count/differential, hemoglobin, hematocrit, blood gases
Electroencephalography
Neuroimaging
Head computed tomography or magnetic resonance imaging
± Lumbar puncture, toxicity screens, serum and urine osmolality, psychiatric examination

Often signs of sympathetic overactivity (tachycardia, elevated blood pressure, tremulousness) and abnormal sleep patterns or "sun-downing" are present.

Mild *behavioral changes* are the earliest manifestations, such as lack of attentiveness to surroundings or a paucity of spontaneous speech, which may give the patient an apathetic or withdrawn appearance. The Mini-Mental State Examination easily reveals mild confusion and can be used to grade the patient's level of cognitive performance sequentially [1]. When there is impaired consciousness, however, this test is unreliable.

The *cranial nerve examination* is focused on pupillary responses, oculomotor function, and respiratory patterns (Table 170.3). As a rule, pupils are small, symmetric, and responsive to light in metabolic causes of obtundation or coma. Noteworthy exceptions to this are anticholinergic poisoning (e.g., atropine, scopolamine), which produces dilated sluggish pupils, and glutethimide (Doriden) poisoning, which results in mid- to large-sized sluggish or fixed pupils [2]. Ocular movements are usually unaffected initially, with eyes in midline position or slightly deviated outward and upward at rest (Bell's phenomenon). Doll's eye maneuvers produce conjugate deviation of the eyes opposite to the direction of head rotation. As the level of brainstem suppression progresses to coma, these responses may disappear completely, especially with an overdose of sedative drugs. In the face of hyperpnea and decerebrate

TABLE 170.2

SIGNS AND SYMPTOMS OF BRAINSTEM CEREBROVASCULAR ACCIDENT (CVA) AND METABOLIC ENCEPHALOPATHY

	Brainstem CVA	Metabolic encephalopathy
Patient profile	Known vascular disease	Organ failure
	Hypercoagulable state	Subacute onset(> 8 h) except in hypoglycemia
	Acute onset (< 8 h), usually > 50 y	Any age, often > 60 y
Motor involvement	Hemiplegic or paraplegic	Moving all limbs except for hypoglycemia
Sensory involvement	Unilateral facial sensory change, or hemianesthesia	No sensory symptoms
Mental status	Obtunded or agitated	Waxing and waning
Pupils	May have Horner's; may have fixed, dilated pupil	Small, normoactive
Eye movements	Disconjugate, skew deviation, cr N. III, IV, VI paresis	Conjugate, midline
Respirations	Apneustic, central hyperpnea, ataxic	Normal, hyperpneic + brief apnea

rigidity, the preservation of doll's eyes is a useful sign pointing to a metabolic, rather than anatomic, cause of coma.

Changes in the respiratory pattern are the next most important findings for the diagnosis of metabolic encephalopathy, also providing a clue as to its etiology. In the mildly confused patient, breathing may be normal, but lethargic or mildly obtunded patients tend to hyperventilate, with brief spells of apnea. This is due to transient lowering of the partial pressure of carbon dioxide (PCO_2) below 15 mm Hg without the appropriate CNS drive to breathe more rapidly at a lower tidal volume. After 12 to 30 seconds of apnea, the cycle of hyperventilation appears again, resulting in a pattern of "periodic respirations" [3]. Hypoventilation is usually seen with depressant drug overdoses, chronic pulmonary failure, and metabolic alkalosis of any cause. Cheyne-Stokes respiration, a rhythmic cycle of waxing and waning hyperpnea/apnea, is another pattern that is occasionally seen in metabolic encephalopathy caused by uremia or hypoxia, but more commonly this indicates bilateral structural lesions of the cortex. Other neurogenic respiratory patterns, such as constant or "central" neurogenic hyperventilation, cluster breathing, and ataxic breathing, are signs of brainstem dysfunction due to structural damage or suppression by barbiturates. These changes are seen only when the patient is stuporous or comatose.

Abnormal motor activity is characteristic of many metabolic encephalopathies and is quite varied in appearance; tremors, myoclonus, asterixis, rigidity, and choreoathetosis may be seen. Tremors are rhythmic, involuntary oscillatory movements seen in all limbs and often exaggerated during voluntary movement. Tremors occur most often in early hypoglycemic encephalopathy, thyrotoxicosis, acute uremia, chronic dialysis encephalopathy, hypercapnia, and drug intoxication, especially with sympathomimetic agents.

Myoclonus is multifocal, appearing as brief shock-like contractions of large muscle groups. Synchronous myoclonic jerks in all limbs can be seen in any patient who is slipping in and out of a drowsy sleep—also known as *sleep-onset myoclonus*. This is often seen in patients who are receiving large doses of narcotics. Multifocal myoclonus, in contrast, is seen in hypoxic–ischemic encephalopathy, chronic hepatic failure of all types, uremia, pulmonary failure, and intoxication with methaqualone and psychedelic agents [4].

Asterixis is a flapping movement produced by unsustained muscle contraction against gravity. Rhythmic extension and flexion of the outstretched limb is present, which disappears at rest. The most common setting for this is in hepatic encephalopathy of any cause, frequently with flapping of the hands, feet, jaw, and tongue. Subacute uremia and pulmonary failure produce asterixis accompanied by myoclonus, which presents a picture of almost constant muscular jerking movements.

Rigidity or generalized muscle spasms are states of constant muscle contraction that are seen when the degree of metabolic encephalopathy is more severe and leads to stupor or coma. This can be the result of end-stage hepatic failure, hypoglycemia (< 25 mg glucose per dL) lasting more than a few minutes, acute renal failure, hyperthermia, and hypothermia below 92°F rectally. Rigidity with dystonic posturing is a clue to amphetamine or phenothiazine poisoning. Choreoathetosis, on the other hand, occurs in chronic hepatic failure, subacute bacterial endocarditis, post-hypoxic insult, Reye's syndrome, chronic dialysis, chronic hypoglycemia, and chronic hyperparathyroidism, appearing as a nonpatterned sequence of twisting or dance-like limb movements.

The *reflex examination* often reveals diffuse hyperreflexia, symmetric except in limbs that were previously affected by a structural lesion. Plantar responses, also known as the Babinski reflex, are typically extensor in both feet and can be elicited easily. In contrast, the sensory examination is usually not affected, but is unreliable if the patient is agitated or obtunded. Response to pinprick, painful pinch/pressure, or a cold stimulus on the limbs is the most useful in demonstrating a grossly intact sensory arc.

Abnormal autonomic responses in metabolic encephalopathy may demand intervention and can cause significant morbidity and mortality. Hypotension, unresponsive to volume expansion, points to intoxication with barbiturates or opiates, myxedema, or Addisonian crisis. In this setting, occult sepsis must always be ruled out before treating for specific metabolic derangements. Fever and leukocytosis may be absent in very debilitated patients. Examination of urine, blood cell counts and coagulation factors, blood and sputum cultures, chest x-ray, and a lumbar puncture are essential to rule out infection. If there remains any doubt about the cause of hypotension, empiric antibiotics, naloxone hydrochloride (Narcan) for possible opiate overdose, intravenous (IV) glucose (1 ampoule), and pressor agents should be added to other supportive measures acutely while the cause is being investigated.

Seizures are another significant symptom of metabolic encephalopathy, especially in uremia, hypoglycemia, pancreatic failure, and various types of metabolic acidosis (e.g., ethylene glycol, salicylates, and so forth). They occur most often at the onset of the metabolic disturbance, for example, as the blood urea nitrogen (BUN) is climbing acutely, and as a preterminal expression of severe neuronal injury in a comatose patient. Management of the seizures is typically ineffective until the underlying cause is corrected. In renal failure, however, one third to half of the standard loading doses of phenytoin or phenobarbital may be all that is needed to control seizures. The interictal electroencephalogram (EEG) serves as a guideline to the need for continued treatment once the encephalopathy has cleared or has become chronic and stable. A persistent focus of epileptiform activity warrants further investigation and anticonvulsant therapy.

The *laboratory investigation* of patients with delirium or coma is crucial in defining the cause of a metabolic encephalopathy. Blood tests for glucose, electrolytes, and blood gases should be drawn immediately along with a panel of hepatic function tests [ratio of serum alanine aminotransferase to serum aspartate aminotransferase, lactate dehydrogenase, ammonium ion (NH_4^+)], BUN, and creatinine. Serum and urine osmolality, cerebrospinal fluid (CSF) analysis, serum magnesium and phosphate levels, and specific hormone levels may be needed to define the cause of encephalopathy further. Careful review of all medications taken before and during hospitalization may direct attention to toxicology screens of blood and urine. The general toxicology screen should be sensitive to opiates, benzodiazepines, caffeine and salicylates, theophylline, barbiturates, and alcohol. Additional drug levels should be ordered if their use is known or suspected (e.g., digoxin, cocaine, phenytoin, and so forth). If there has been a sudden change in mental status, a bolus of 25 g glucose should be administered intravenously without hesitation to avoid prolonged hypoglycemia.

In general, the EEG in metabolic encephalopathy is abnormal; background slowing is the most common pattern found (< 9 Hz) [5]. Other patterns can also be useful in identifying or corroborating the cause of the encephalopathy. Slow activity that is prominent frontally, with deep triphasic waves (in the 2- to 4-Hz range), is characteristic of hepatic encephalopathy but can be seen in renal failure too [6]. This has also been reported in levetiracetam toxicity [7], hyperammonemic states due to gastroplasty [8] and ureterosigmoidostomy [9], and rare metabolic disorders such as ornithine transcarbamylase deficiency [10]. Spreading of the slow activity toward the occipital leads is a sign of deepening coma in this setting. Bursts of high-voltage activity amidst normal background frequencies are also a sign of diffuse metabolic disturbance. More importantly, the EEG in a patient with an acute encephalopathy of unknown cause may reveal subclinical (electrical) status epilepticus,

warranting urgent and aggressive anticonvulsant treatment. This is particularly common in the case of alcoholics and diabetics, who are at risk for multiple CNS insults.

Neuroimaging [computed tomography (CT) or magnetic resonance imaging (MRI)] scans are often crucial in situations in which there is rapid deterioration of mental status without focal signs or an obvious metabolic cause such as hypoglycemia. Most mass lesions, such as subdural hematomas or brain tumors, are evidenced clinically by a rostrocaudal progression of neurologic signs. The initial picture may be nonfocal with obtundation, but this is followed sequentially by flexor or extensor posturing on one or both sides and then the loss of pupillary or caloric responses. Later, medullary respiratory patterns or bradycardia appear. A noncontrast head CT or MRI is definitive in many cases but does not always distinguish a brainstem stroke. Early consultation by a neurologist is crucial, especially when the cause of impaired consciousness is not clearly due to a metabolic disorder. Transient changes in vascular permeability associated with Wernicke's encephalopathy can manifest as vasogenic edema in the brainstem periaqueductal and fourth ventricular areas along with contrast enhancement of the mammillary bodies [11].

Lumbar puncture is also indicated when there is a rapid onset of encephalopathy, especially with a fever, headache, or meningismus. Occult subarachnoid hemorrhage, infection, or elevated intracranial pressure may be found in the absence of funduscopic changes or clear-cut clinical history. Ideally, the lumbar puncture should be performed atraumatically with a small (22-gauge) spinal needle and a simultaneous sample of serum obtained to compare glucose and protein levels in the blood and CSF.

ETIOLOGY

Hepatic Failure

The clinical onset of *hepatic encephalopathy* may be subtle, with a blunting of affect and lethargy, or dramatic in 10% to 20%, with mania or an agitated delirium [12]. It is easy to recognize hepatic encephalopathy in an individual with the obvious stigmata of chronic liver disease, such as ascites, varices, or jaundice. In those without apparent liver disease, the mental changes may only appear after an additional metabolic demand on the liver. Such stressors are a high-protein meal, gastrointestinal bleeding with increased blood absorption from the gut, or hepatically metabolized drugs [13]. Sedatives and acetazolamide are particularly offensive in this situation.

Asterixis is the next most common clinical sign, appearing in all limbs, the jaw, and the tongue. As the patient progresses into a coma, it may be replaced by muscle spasticity and decorticate or decerebrate posturing to stimulation. The Babinski responses are present (extensor plantar reflexes), and gaze-evoked ocular movements are variable at this stage; pupillary responses are always preserved. Oculocephalic and vestibulo-ocular (caloric) responses remain until the patient is moribund. Hyperventilation is another consistent sign of hepatic encephalopathy and results in respiratory alkalosis. The ocular, pupillary, and respiratory patterns above help to distinguish severe hepatic encephalopathy from space-occupying lesions of the cortex and brainstem.

The pathophysiology of hepatic coma is not certain, but it is thought to be caused by portacaval shunting of neurotoxic substances. These putative toxins include excess ammonia, large molecules normally excluded by the blood–brain barrier [14], increased water, and the "false" neurotransmitter octopamine [15]. Hypoglycemia, as a result of decreased glycogen stores in the liver, may complicate the CNS picture.

The serum transaminases are usually elevated two- to threefold, and serum ammonia is at least in the high normal range once the patient is lethargic—with a linear correlation thereafter between higher laboratory values and lower cognitive state. The CSF remains normal until the serum bilirubin exceeds approximately 5 mg per dL, which tints the fluid yellow. The EEG characteristically shows progressive slowing from the frontal to the occipital leads as coma deepens. Triphasic waves are seen in most cases but are not pathognomonic.

Therapy for hepatic encephalopathy is directed toward decreasing the amount of toxic substances that are being shunted to the brain. Neomycin and lactulose help to sterilize and flush the gut. A protein-restricted diet and the exclusion of hepatically cleared drugs decrease the metabolic load, and IV glucose effectively maintains the serum glucose level. Neurologic recovery then depends on the capacity of the liver to regenerate at least 25% of its full function. With prolonged or repeated bouts of hepatic coma, there may be persistent, irreversible signs of basal ganglia dysfunction evidenced by chorea, postural tremors, or a parkinsonian picture (acquired hepatocerebral degeneration) [16].

Reye's Syndrome

Reye's syndrome is a unique and quite morbid form of acute hepatic encephalopathy seen in children, usually between ages 1 and 10 years. It occurs in the clinical setting of an acute viral infection, for example, chickenpox or influenza A or B, plus aspirin therapy [17]. Approximately 4 to 7 days after the viral symptoms start, the child becomes irritable, with vomiting and sometimes with headache or blurred vision. An agitated delirium, combativeness, and progressive obtundation rapidly ensue over hours, followed by hyperventilation, pupillary dilatation, and generalized seizures. Later in the course decerebrate rigidity, Babinski responses, and papilledema may develop as well.

The pathology of Reye's syndrome includes infiltration of the liver and other visceral organs with small fat droplets and diffuse cerebral edema. In cases that are complicated by severe hypoglycemia and seizures, anoxic damage with laminar necrosis of the cerebral cortex is also found. The cause of these changes is presumed to be mitochondrial poisoning, but the pathogenic agent has not yet been identified. Acetylsalicylic acid has consistently been implicated in this cellular damage. This has led to the standard practice of prescribing acetaminophen instead of aspirin for viral symptoms in children, thereby reducing the incidence of Reye's syndrome [18].

The differential diagnosis relies on measurement of liver function and a high index of suspicion in the appropriate setting. The serum transaminases rise three- to fivefold in the first 48 hours, and the serum ammonia is dramatically increased, sometimes into the 200 μmol per L range. Hypoglycemia is also an early sign, aggravating the lactic acidosis and respiratory alkalosis that are seen later in the course.

Treatment for Reye's syndrome is directed toward diminishing the cerebral edema, controlling seizures, and providing adequate electrolytes and glucose for support while the liver is effectively shut down with respect to oxidative metabolism. This is best achieved in an ICU with a standard protocol for Reye's disease using intracranial pressure monitoring and mannitol or glycerol for reduction of intracranial pressure [19].

The prognosis in recent years has improved markedly; mortality and morbidity are now 10% to 20%, as opposed to 40% to 50% two decades ago. Factors that contribute to a poor outcome are age less than 1 year, serum ammonia levels more than five times normal at their peak, and a prothrombin time more than 20 seconds. Other negative prognostic indicators are renal failure and a very rapid progression of liver failure

in the first 48 hours. Early intervention is the key to a good outcome neurologically and systemically.

Renal Failure

Uremic encephalopathy may develop acutely, be superimposed on chronic renal insufficiency, or occur as a consequence of chronic dialysis. It is often a complication of systemic diseases that independently affect the kidneys and the CNS such as collagen-vascular disease, malignant hypertension, drug overdoses, diabetes, or bacterial sepsis. The clinical picture is initially variable and does not correlate directly with measures of renal failure such as BUN and creatinine.

The first sign of encephalopathy in uremia is delirium or a decrease in level of consciousness; hyperventilation and increased motor activity follow as the patient becomes obtunded. Also, there is a high frequency of generalized convulsions at the outset and a metabolic acidosis with low serum bicarbonate. The motor component is prominent in many patients with multifocal myoclonus, hypertonus or asterixis, and tremors, together producing a picture of "twitch-convulsif"—as if the patient had fasciculations [20]. Oculomotor function and pupillary responses are normal, but deep tendon reflexes may be asymmetric, and focal weakness often occurs, with shifting hemiparesis during a single period of encephalopathy. The variability of focal motor signs helps to rule out a structural lesion but does not obviate the need to look for multifocal seizures in a patient with overt twitching and depressed consciousness.

Studies of the effect of uremia on neuronal function have not been able to demonstrate a direct correlation between the cognitive state and levels of BUN or with any other biochemical or electrolyte markers. The EEG, although becoming slower with higher levels of BUN, also does not correlate with mental status changes, especially in chronic uremia [21]. Hence, the pathophysiology of uremic encephalopathy is not known.

The major diagnostic differential to consider is between a hypertensive crisis and uremic encephalopathy, because malignant hypertension often leads rapidly to renal failure and neurologic signs. Evidence of papilledema, retinal vasospasm, and cortical blindness or aphasia, with a diastolic blood pressure of more than 120 mm Hg, argues strongly for a hypertensive crisis. In contrast, a sudden rise of BUN alone is most consistent with uremic encephalopathy.

Two variants of this disorder are seen in patients on peritoneal dialysis or hemodialysis. The *acute dialysis dysequilibrium syndrome* is seen in children more often than in adults undergoing hemodialysis with large exchanges of dialysate. A sudden shift of solutes out of the vascular compartment produces a hyperosmolar state in the brain and subsequent water resorption intracerebrally. This results in water intoxication, with florid encephalopathy within 30 to 60 minutes. Slower dialysis obviates the problem in general [22].

Dialysis dementia is insidious by comparison and is evidenced by post-dialysis lethargy, asterixis, myoclonus, dysphasia, and progressive loss of cognitive abilities over years. This disorder has been linked to increased amounts of aluminum in the dialysate augmented by aluminum-containing antacids in the diet [23]. Although the brains of patients with this disorder do not contain excess aluminum compared to those of other dialysis patients, elimination of aluminum from these sources helps reverse the symptoms in the early stages. This syndrome is now relatively rare.

Pulmonary Failure

A combination of *hypoxemia* and *hypercarbia* can produce typical changes of a metabolic encephalopathy in patients with underlying pulmonary failure. Individuals with chronic obstructive pulmonary disease, for example, tolerate a PCO_2 of 50 to 60 mm Hg without mental status changes. However, a sudden increase of PCO_2 of up to 65 to 70 mm Hg due to hypoventilation, or impaired oxygen exchange, can lead to lethargy, headaches, and a rise in intracranial pressure. Associated signs are papilledema or retinal vein congestion, extensor Babinski signs, asterixis, myoclonus, and, often, generalized tremors. Seizures are rarely seen, and pupillary and oculomotor functions are preserved unless there is a concomitant hypoxic–ischemic insult [24].

This course of events may be precipitated by systemic infection with fatigue of ventilatory muscles, paralysis of these muscles by neuromuscular disease or Guillain-Barré syndrome, and sedative drugs with their depressant effect on the medullary respiratory center. In the well-compensated hypercarbic individual, oxygen therapy may be counterproductive by decreasing respiratory drive from the medulla. Rapid correction of hypercarbia by artificial ventilation, on the other hand, exacerbates the compensatory chronic metabolic alkalosis that these patients have, possibly resulting in a further depression of mental status plus seizures [25].

The critical factor in the development of pulmonary encephalopathy is a rapid increase in serum PCO_2. This may be complicated by the presence of sedatives, hypoxemia, cardiac failure, and renal hypoperfusion. Treatment is directed toward slow correction of hypercarbia while maintaining an adequate PO_2 and good cerebral blood flow. Prognosis for full neurologic recovery is good if the patient is not subjected to cerebral ischemia as well.

Hypoglycemic Encephalopathy

Hypoglycemia can occur as an isolated problem or as a complication of liver failure, of tumors producing insulin-like substances, or of urea cycle defects. The most common case is that of a diabetic with an accidental or deliberate overdose of insulin or oral hypoglycemic agents. An initial insulin reaction occurs when the serum glucose drops below approximately 40 mg per dL, producing flushing, sweating, faintness, palpitations, nausea, and anxiety. This persists for several minutes before the patient becomes confused and either agitated or drowsy [26]. Focal neurologic signs such as hemiparesis, cortical blindness, or dysphasia may appear at this point, mimicking an acute stroke [27]. If the serum glucose drops precipitously below 30 mg per dL, generalized convulsions may occur in flurries followed by a postictal coma. Prompt correction of the hypoglycemia at this point leads to reversal of the neurologic deficits, but repeated episodes can result in a subtle dementia evolving over many years [28].

When severe hypoglycemia is sustained for more than 10 minutes, stepwise progression of neurologic signs occurs. The first step is motor restlessness with frontal release signs such as sucking, grasping, and a tonic jaw jerk. Next, diffuse muscle spasms appear and sometimes myoclonic jerks. Finally, decerebrate rigidity is seen before the so-called medullary phase of hypoglycemia. The *medullary phase* describes a state of deep coma with dilated pupils, bradycardia, hypoventilation, and generalized flaccidity, much like hypoxic–ischemic coma. The pathologic changes associated with bouts of hypoglycemic encephalopathy are also similar to hypoxic–ischemic insults, although the cerebellum is relatively spared [29].

Differentiating hypoglycemic coma from a seizure disorder, a cerebrovascular accident, or a drug overdose is not possible at the outset unless stat serum glucose is obtained before IV fluids are administered. One should not delay treatment with a bolus of 50 mL 50% glucose (1 ampoule) if there is doubt about the cause of a rapidly evolving coma, because hypoglycemic

encephalopathy can result in permanent neurologic deficits if not reversed in 20 minutes or less. The first bolus of glucose must be followed by close monitoring of blood glucose levels, because most agents that lead to symptomatic hypoglycemia are long acting [30].

Hyperglycemic Encephalopathy

Hyperglycemia that is severe enough to produce mental status changes rarely occurs in isolation from other metabolic disturbances. Hypokalemia and hypophosphatemia, hyperosmolality and ketoacidosis, or lactic acidosis often accompany serum glucose levels more than 300 mg per dL. In contrast, acidosis may be absent in nonketotic hyperglycemic hyperosmolar states, whereas the serum osmolality is often more than 350 mOsm per kg and serum glucose more than 800 mg per dL. The neurologic changes in any case appear to correlate best with abnormalities of serum osmolality and the rate at which it is corrected [31]. In juvenile or "brittle" diabetics, ketoacidosis develops after a dose of insulin is missed or an occult infection occurs. The first changes are mild confusion, lethargy, and deep regular inspirations (Kussmaul's breathing) in addition to signs of dehydration. Elderly patients are more prone to nonketotic hyperglycemia, especially when they have an inadequate diet, take medications that interfere with insulin metabolism [e.g., phenytoin (Dilantin), steroids], or take oral hypoglycemic agents [32]. Lactic acidosis may be present, in particular, with phenformin. These patients also tend to have focal or generalized seizures and transient or shifting hemiplegia as the level of coma deepens. The preservation of pupillary and oculocephalic responses helps to identify the clinical picture in such cases as being metabolic rather than structural.

The hyperosmolality occurring with hyperglycemia of any type causes a shift of water from the intracerebral to intravascular space with resulting brain shrinkage [33]. How this produces the neurologic changes observed is not known. More importantly, rapid correction of hyperosmolality by IV hydration and insulin results in cerebral water intoxication and signs of increased intracranial pressure. This is exemplified by the patient who begins to awaken from a hyperglycemic coma during IV therapy but later develops a headache and recurrent lethargy and seems to drift back into the previous state. Significant morbidity and mortality follow if these fluctuations are not observed and the IV treatment is modified appropriately [34]. Other details of the management of diabetic coma are addressed in Chapter 101.

Other Electrolyte Disturbances

Hyponatremia and *hypernatremia* cause fluid shifts and critical changes in serum osmolality, with the same effects on cerebral dysfunction as those described above. Mild to moderate *hyponatremia* (120 to 130 mEq per L) is evidenced by confusion or delirium with asterixis and multifocal myoclonus. If the serum sodium goes below 110 mEq per L, or drops at a rate more than 5 mEq per L per hour to 120 mEq per L and below, seizures and coma are likely to follow. This course of events portends permanent neurologic damage even after careful therapy [35]. Common causes of hyponatremia are (a) the syndrome of inappropriate antidiuretic hormone secretion (SIADH), with myriad etiologies; (b) excess volume expansion with hypotonic IV solutions; and (c) renal failure with a decreased glomerular filtration rate [36]. Other less common causes include psychogenic polydipsia, severe congestive heart failure, and Addison's disease.

The neurologic signs of hyponatremia are nonspecific, and the general approach to evaluation of an encephalopathy often identifies the problem. Treatment is directed toward the underlying cause with fluid restriction in mild cases, unless total body sodium is depleted. In moderate cases (i.e., a serum sodium of 105 to 115 mEq per L), PO sodium supplementation may be needed as well. A serum sodium below 100 mEq per L is life threatening. This requires judicious treatment with IV hypertonic saline at a rate calculated to replace about half of the total sodium deficit in 3 to 6 hours (averaging less than or equal to 0.5 mg Na^+ per hour). The remainder of the deficit should be administered in the next 24 to 48 hours [37]. Excessively rapid correction of severe hyponatremia, especially in alcoholic or malnourished individuals, can be associated with another serious neurologic complication known as *central pontine myelinolysis* [38]. Central pontine myelinolysis starts with a flaccid quadriparesis and inability to chew, swallow, or talk, or "locked-in syndrome" developing over a period of days. Patients who recover from the underlying systemic disorder are left with a spastic paraparesis and pseudobulbar speech; some may improve over several months.

Hypernatremia is not seen very often outside the hospital setting except in children with severe diarrhea and inadequate PO fluid intake. Excess diuretic therapy, hyperosmolar tube feedings, and restricted access to PO fluids are reflected in a serum sodium of more than 155 mEq per L in institutionalized patients. Clinically, one sees progressive confusion and obtundation in subacute cases. With levels of sodium more than 170 mEq per L developing acutely, the brain may shrink, and subdural hematomas can occur as a result of stretching of the dural vessels. These patients may complain of headache, develop seizures, or simply drift into a stupor. Catastrophic complications such as venous sinus thrombosis and irreversible coma are seen with a serum sodium level of more than 180 mEq per L due to the marked hyperosmolality that accompanies it.

The cause of profound hypernatremia is often diabetes insipidus, which may be secondary to head trauma. Impaired thirst mechanisms or depressed consciousness interfere with the polydipsia that is pathognomonic of diabetes insipidus [39]. The treatment of symptomatic hypernatremia depends on its cause: dehydration alone or complicated by additional sodium depletion due to hyperosmolar diuresis or excessive sweating. Fluid replacement is accomplished with 5% dextrose and water at a rate dependent on the total body water deficit—half of the water needed being administered IV in the first 12 to 24 hours and no faster. Saline solutions of half normal strength (0.45%) are used in most other cases. The exception is hyperosmolar diabetic coma, in which insulin and normal saline are both necessary to correct the severe serum hypertonicity.

Metabolic acidosis by itself produces only mild delirium or confusion [40] but may be accompanied by organ failure, direct CNS toxicity from drug metabolites, or volume depletion. The first sign of an encephalopathy caused by metabolic acidosis is hyperpnea followed by mental status changes and mild muscular rigidity. Ingestion of toxic doses of poisons such as methanol, ethylene glycol, and salicylates result in encephalopathy along with low serum bicarbonate levels (less than 15 mEq per L) [41]. Therapy must be directed toward vigorous correction of the metabolic acidosis while the specific cause is being elucidated.

Pancreatic Failure

Acute pancreatitis rarely leads to mental status changes during the initial bout. When recurrent or chronic, symptoms of encephalopathy may prominently wax and wane [42]. The clinical presentation is abdominal pain followed over 2 to 5 days by hallucinosis, delirium, focal or generalized seizures, and bilateral extensor Babinski responses. As the serum amylase continues to rise, the patient may lapse into a coma as

a result of secondary hyperglycemia, hypocalcemia, and hypotension. The exact cause of the encephalopathy is unknown; the prognosis and treatment depend on the underlying cause and severity of the pancreatitis [43].

Endocrine Disorders

Adrenal disorders are an important consideration in acute encephalopathy, because hypo- and hyperadrenalism produce alterations in CNS function.

Addison's disease or *secondary adrenocortical deficiency* occurs acutely in the setting of septicemia, surgery, and, most frequently, sudden withdrawal of chronically administered steroids. In the latter, one does not see the stigmata of chronic adrenocorticotropic hormone deficiency but rather hypotension, a mild hyponatremia, hypoglycemia, and hyperkalemia, together with a delirium or stupor that fluctuates erratically [44]. The electrolyte disturbances in most cases are not severe enough to explain the encephalopathy; other pathologic mechanisms such as cerebral hypoperfusion or water intoxication have been suggested. Unlike many metabolic encephalopathies, adrenocortical insufficiency is associated with *decreased* muscle tone and deep tendon reflexes. Seizures and papilledema may appear when the patient has a profound adrenocorticotropic hormone deficiency and coma. The neurologic picture does not clear until cortisone replacement is given along with treatment of the electrolyte imbalances. These patients are also particularly sensitive to sedative medications and may lapse into coma with small doses of narcotics or barbiturates [45].

Excess steroids produce different forms of encephalopathy depending on whether the source is endogenous or exogenous. In Cushing's disease, psychomotor depression and lethargy are the norm, whereas high doses of prednisone usually cause elation, delirium, or frank psychosis [46]. The latter is not uncommon in the ICU setting due to the administration of stress levels of steroids and multiple other CNS toxins. The behavioral changes are key to recognizing this problem because there are no specific metabolic markers [47]. Treatment consists of withdrawal of the steroids and sometimes temporary use of tranquilizers or lithium for the psychiatric features as well. Full neurologic recovery may lag behind the treatment by several days to weeks.

Hypothyroidism is now a rare cause of encephalopathy and coma. It may be confused initially with other causes of hypotension, hypoventilation, and hyponatremia, such as septic shock, brainstem infarcts, or an overdose of sedatives. The diagnosis should be considered in any patient with hypothermia, pretibial edema, pseudomyotonic stretch reflexes (e.g., delayed relaxation of the knee jerk), and coarse hair or facies. Muscle enzymes, serum cholesterol, and lipids may be elevated along with the thyroid-stimulating hormone level [48]. Diagnostic confirmation is often delayed pending results of thyroid function tests, but replacement therapy should be initiated early with IV triiodothyronine or thyroxine. The constitutional symptoms may take several weeks to respond, but the neurologic picture clears promptly with proper treatment. Another form of hypothyroid associated encephalopathy is seen in Hashimoto's thyroiditis with a subacute subtle change in personality, memory deficits, and cerebellar ataxia accompanied by cerebellar atrophy on imaging studies. Confirmation of the diagnosis requires specific tests for antithyroglobulin and antithyroperoxidase antibodies along with an elevated TSH. Treatment with thyroid replacement therapy often results in recovery over a few months.

Thyrotoxicosis is more difficult to recognize because it can present in an apathetic form, as a thyroid storm, or in a subacute form. Elderly patients are more likely to appear depressed or stuporous and without evidence of hypermetabolism [49]. The key to the diagnosis in such cases is evidence of recent weight loss and atrial fibrillation, often with congestive heart failure and a proximal myopathy. In a thyroid storm, the patient with indolent hyperthyroidism may be stressed by an infection or surgery and responds with marked signs of hypermetabolism: tachycardia, fever, profuse sweating, and pulmonary or congestive heart failure. Neurologically, the individual becomes acutely agitated and delirious and then progresses into a stupor [50]. The subacute picture that precedes this is one of mild irritability, nervousness, tremors, and hyperactivity and is often misconstrued as an affective disorder rather than endocrine in origin. Ophthalmologic signs such as proptosis, chemosis, and periorbital edema are useful in identifying this form of thyrotoxicosis.

Therapy for thyrotoxic encephalopathy is aimed at ablation of the gland, but supportive care may require beta-blockers, digoxin, diuretics, and sometimes dexamethasone and sedatives for the associated hypermetabolic state. Encephalopathy is also seen in disorders of the pituitary gland and parathyroid gland, although rarely as a primary process. *Hypopituitarism* may result from radiation or surgery to the area of the sella and can present as a chronic encephalopathy with features of thyroid or adrenal insufficiency, or both. An acute coma due to infarction or hemorrhage of the pituitary gland, known as *pituitary apoplexy*, can be seen in acromegalics with large adenomas or in patients with postpartum hemorrhage and hypotension (Sheehan's syndrome) [51]. Subarachnoid blood and ocular abnormalities plus signs of increased intracranial pressure help to identify the lesion in such cases. Encephalopathy from *hyperpituitarism* reflects the specific neurohumoral substance that is being released in excess and does not represent a unique syndrome.

Hyperparathyroidism may be manifest neurologically with asthenia or a vague change in personality. The patient is mildly depressed, lacks energy, and fatigues easily. A serum calcium more than 12 mg per dL and elevated parathormone levels are important diagnostic findings. Occasionally, psychiatric symptoms predominate, starting with delirium and psychosis, or obtundation and coma when the serum calcium exceeds 15 mg per dL. Hypercalcemia caused by metastatic bone lesions, paraneoplastic parathormone-like substances, sarcoidosis, primary bone diseases, and renal failure are associated with a subacute or chronic encephalopathy similar to hyperparathyroidism. Treatment in these cases must be directed toward the underlying disease rather than addressing the hypercalcemia alone. Primary hyperparathyroidism is effectively managed by ablation of the overactive gland. This is not always possible, because the glands often are ectopic and may escape discovery on selective angiography or exploratory surgery.

Hypocalcemia due to *hypoparathyroidism* produces an encephalopathy that parallels the depression of serum calcium levels. At less than 4.0 mEq per L calcium, a blunted effect and seizures are common and may be confused with a dementing process or epilepsy. The motor signs of hypocalcemia, that is, tetany or neuromuscular irritability, should make one suspicious of a metabolic disturbance [39]. Another diagnostic dilemma is the occasional presentation of hypocalcemia with papilledema and headache. The opening pressure on lumbar puncture is elevated to the same degree as in pseudotumor cerebri, but a head CT is likely to show basal ganglia calcifications [48]. Furthermore, the presence of cataracts and mental dullness in a previously normal individual should lead one to check the serum calcium and parathormone levels.

The mechanism by which hypocalcemia and hypoparathyroidism produce these varied neurologic symptoms is not known. Replacement of serum calcium by dietary means is usually inadequate to correct the CNS disorder. Supplementation with vitamin D and calcitriol enhances the absorption and utilization of oral calcium.

Other Causes of Encephalopathy

The list of causes of diffuse or metabolic encephalopathies is so lengthy that the problem of diagnosis must be resolved by a process of elimination. Drugs and toxins lead all other possible causes, with a frequency of approximately 50% (see Chapters 117 through 145). Hepatic, renal, or pulmonary failure is causative in another 12% and endocrine or electrolyte disturbances in approximately 8%. Other less common etiologies include thiamine deficiency (Wernicke's encephalopathy), cardiac bypass surgery, subacute bacterial endocarditis, and hyperthermia. All of these disorders produce microembolic or microhemorrhagic/petechial lesions in specific areas of the brain.

Wernicke's encephalopathy develops acutely in the clinical setting of an alcoholic or a malnourished individual, especially when IV glucose solutions without vitamin supplementation are given. Because thiamine is a cofactor in the utilization of cerebral glucose, it is depleted by the IV infusion [52]; confusion, obtundation, and loss of short-term memory rapidly ensue. The hallmark of this entity is a striking impairment of ocular movements, causing an external ophthalmoplegia, nystagmus, and diminished oculocephalic responses. Prompt IV and PO administration of 100 mg thiamine restores ocular function completely. The cerebral symptoms resolve slowly with the addition of 100 mg PO thiamine daily for 3 days or more. If untreated, the patient may lapse into a coma due to autonomic failure with accompanying shock and hypothermia and often dies. Repeated or untreated episodes of Wernicke's disease may result in a chronic Korsakoff's psychosis with profound memory impairment [49].

More recently, recognition of autoantibodies to potassium channels (VGKC-Ab) and NMDA receptors presenting with a subacute limbic-type encephalopathy has led to exciting research into the role of channel blockade in reversible mental status changes. In many cases, there is no evidence of an occult cancer (e.g., testicular or ovarian in young people) and the prognosis with immunoglobulin or steroid therapy is good [50].

Hyperthermia due to heat stroke also has a characteristic clinical setting—young individuals experiencing excessive sweating caused by overactivity and elderly people receiving anticholinergics who are exposed to a hot environment [51]. In both cases, neurologic changes occur when the core body temperature reaches 42°C (107.6°F). The patient may become agitated and confused with intermittent generalized seizures or may immediately lapse into a coma as if due to a stroke. The presence of tachycardia, hot and dry skin, and diffuse hypertonus occurring in the appropriate circumstances identifies the likely etiology. Normal pupillary size and reflexes (except with anticholinergics) and oculocephalic responses, and the absence of focal motor signs also point to a nonstructural lesion. However, if the core body temperature is not lowered early in the course, the patient may be left with sequelae similar to those seen in hypoxic–ischemic encephalopathy. Other causes of temperature more than 42°C are rare and are not discussed here [53].

Up to 20% of patients with *bacterial or marantic endocarditis* can present with a subacute encephalopathy manifested by confusion and hyperpnea with or without fever [54]. It should be suspected in any patient with Gram-negative sepsis [37]; ovarian cancer; malignant melanoma; adenocarcinoma of the lung, breast, prostate, or pancreas; and an immunocompromised state. Definitive diagnosis rests on the blood culture results and an echocardiogram showing vegetations. Treatment is directed toward reducing or removing the cardiac source.

CONCLUSIONS

Metabolic encephalopathy is one of the most frequently seen neurologic disorders in the ICU arena. It is also one of the most diverse in its clinical presentations and requires a systematic approach to define the etiology and to institute effective treatment. The features that distinguish most metabolic encephalopathies from structural lesions are (a) a nonfocal neurologic examination, (b) increased motor activity, (c) intact ocular and pupillary reflexes, and (d) laboratory abnormalities that support the clinical picture. Additional tests such as an EEG, head CT, or toxicology screen are useful in ruling out other possible causes.

One should keep in mind that many patients in the ICU have an underlying chronic encephalopathy due to long-standing illness [56]. Therefore, they are more susceptible to minor metabolic perturbations induced by small doses of drugs, slight shifts of fluid balance, or worsening organ failure. Early recognition and correction of such factors improve the patient's prognosis for a full neurologic recovery. Toward this end, it is prudent to consult the neurologist before the complications of multiple treatments and further changes confound the clinical course.

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CHAPTER 171 ■ GENERALIZED ANOXIA/ ISCHEMIA OF THE NERVOUS SYSTEM

CAROL F. LIPPA AND MAJAZ MOONIS

Anoxic brain injury results from inadequate oxygen supply to the brain. The clinical picture ranges from mild confusion to deep coma with loss of brainstem responses. Anoxic damage can be caused by circulatory collapse, respiratory failure, or inadequate hemoglobin binding to oxygen. Prognosis and management of the anoxic patient depend in part on which of these mechanisms has caused the injury.

PATHOGENESIS

The brain is unique in that it uses almost exclusively aerobic metabolism of glucose. The continuous availability of oxygen is secured by the cerebral vasculature's autoregulatory mechanism [1], which controls the rate of blood flow over a wide range of blood pressures. If blood pressure drops too low for autoregulatory mechanisms to operate, oxygen extraction from the blood increases. Failure of this compensatory mechanism results in a changeover from aerobic to anaerobic metabolism.

In cardiac arrest, depletion of brain oxygen reserves occurs within 10 seconds, thereby eliminating the major source of neuronal energy from ATP (adenosine triphosphate) and phosphokinase. Excessive glutamate release and reduced reuptake lead to activation of the NMDA (*N*-methyl-d-aspartate) receptors and consequent ischemic cascade. The resulting intracellular (cytotoxic) edema leads to increased intracranial pressure.

The changeover to anaerobic metabolism results in neuronal catabolism. In cardiovascular collapse, loss of venous outflow leads to the accumulation of lactic acid and pyruvate, the end products of anaerobic metabolism. Buildup of these catabolites potentiates the cellular damage.

DIAGNOSIS

The first question to address when evaluating a comatose or obtunded patient with a possible hypoxic insult is whether the impaired consciousness is the result of a metabolic insult or a structural brain lesion. Coma caused by a mass lesion is usually associated with focal neurologic signs. Computed axial tomography (CT) or magnetic resonance imaging (MRI) scans usually reveal focal lesions in this setting. Metabolic causes, including anoxic encephalopathy, should be suspected when patients with impaired consciousness present with a non-focal examination.

The diagnosis is often suggested by the clinical setting (e.g., cardiac arrest in patients with arrhythmias or myocardial infarctions, or severe episodes of intraoperative hypotension). Arterial blood gas determination, if obtained during the causal event, can confirm the diagnosis. A partial pressure of oxygen of less than 40 mm Hg causes confusion and less than 30 mm Hg results in coma [2]. Associated abnormalities that potentiate anoxic damage include anemia, acidosis, hypercapnia, hyperthermia, and hypotension.

The internist or neurologist is often consulted to evaluate the patient who has impaired consciousness after well-documented cerebral hypoperfusion that has occurred during surgical operations requiring the use of extracorporeal circulation. The neurological examination is nonfocal. Because surgical patients with such a history often have preexisting illnesses (vascular disease, borderline renal function, hepatic impairment, diabetes), it is the obligation of the intensive care physician to determine new deficits due to anoxic encephalopathy, or other treatable conditions secondary to metabolic, infectious, and iatrogenic factors such as sedating medications. Intracerebral hemorrhage and subdural hematomas should also be sought, because they can occur spontaneously in the perioperative period, especially in anticoagulated patients.

CLINICAL COURSE AND PROGNOSIS

The clinical outcome of patients with anoxic injuries depends on the degree and duration of oxygen deprivation to the brain as well as the maintenance of blood flow. With complete cessation of blood flow to the brain, consciousness is lost after several seconds. If anoxia is moderately prolonged, the patient awakens but may have residual deficits, such as cognitive impairment, or later sequelae, including extrapyramidal movement disorders or seizures, which may not develop for days to weeks.

A delayed postanoxic syndrome may occur rarely in patients with anoxic insults after the initial coma. Three to 30 days following the initial anoxic insult, after the patient has regained consciousness and cognitive function, there is a secondary decline characterized by irritability, confusion, lethargy, clumsiness, and increased muscle tone; patients may become comatose again and die. This uncommon condition occurs most often in cases of carbon monoxide poisoning. Pathologically, widespread demyelination is seen without gray matter changes. The cause is unknown, but it may be due to alteration of enzymatic processes, edema, or damage to small blood vessels [2,3].

The overall prognosis for a meaningful recovery in patients with nontraumatic coma is guarded; the longer patients are in coma, the worse the outcome [4–6]. Most improvement occurs within the first 30 days. Non-anoxic metabolic coma carries the best prognosis, while anoxic coma has a better prognosis than coma resulting from structural lesions. A good outcome is seen in 50% of patients who awaken within 24 hours. Although infrequent seizures or myoclonus do not affect prognosis, myoclonic or nonconvulsive status epilepticus is a grave prognostic sign and is associated with poor recovery [4,7].

If consciousness is maintained during a hypoxic event, there is rarely permanent brain damage. Irreversible damage is rarely seen in healthy individuals if the duration of anoxia is less than 4 minutes, although it may be incurred in individuals with preexisting cerebrovascular disease in shorter periods.

In cases of nontraumatic coma, the most valuable prognostic information is obtained from the physical examination. Favorable prognostic indicators include

1. Recovery of multiple brainstem responses within 48 hours (pupillary, oculocephalic, and corneal) [4];
2. Return of purposeful responses to painful stimuli by 24 hours;
3. Primary pulmonary event leading to coma;
4. Hypothermia at the time of the anoxic event may be protective; patients who have experienced near-drowning, submerged in cold water up to 40 minutes may return to normal neurologic function [8];
5. Younger age (children and young adults) [9,10].

Poor prognostic indicators in persistent coma include

1. Absence of pupillary or corneal responses, and absent motor response to pain by the third day [11];
2. The loss of vestibulo-ocular responses at 12 hours and the presence of decerebrate or decorticate posturing at 24 hours [5,8];
3. Electroencephalogram (EEG) patterns: nonreactive EEG; burst suppression; alpha coma. Serial EEGs documenting improvement are associated with a better prognosis [12,13];
4. Short-latency somatosensory evoked potential tests are noninvasive tests of the sensory system that are absent in brain death but preserved in severe reversible comas, such as barbiturate coma that can mirror brain death [14,15]. Absent cortical N20 on somatosensory evoked response at 72 hours is associated with irreversible coma. N20 present at 8 hours has a 25% chance of recovery [15,16];
5. The presence of either diffuse edema or watershed infarctions on CT scans;
6. Loss of gray white matter distinction on CT scan and severe abnormalities on diffusion-weighted imaging [17,18];
7. Myoclonus or status epilepticus the first day.

A recent Academy of Neurology Practice Parameter by Wijdicks et al. [19] is an evidence-based review for predicting the outcome in survivors of cardiopulmonary resuscitation. The authors conclude that "Pupillary light response, corneal reflexes, motor response to pain, myoclonus status epilepticus, serum neuron-specific enolase and somatosensory evoked potential studies can reliably assist in accurately predicting poor outcome in comatose patients after cardiopulmonary resuscitation for cardiac arrest."

When prognosticating by the clinical criteria alone, one must be careful that no sedative, anesthetic, or anticonvulsant (Dilantin, phenobarbital) is being used, because these agents can suppress brainstem reflexes.

Respiratory insufficiency with maintained circulation carries a better prognosis. A low partial pressure of oxygen does not necessarily convey a bad prognosis in cases of isolated hypoxia [20] if circulation is carefully maintained [21].

Conversely, the presence of metabolic abnormalities, such as lactic acidosis, worsens prognosis.

In cases of out-of-hospital cardiac arrest, survival depends on the total time required to establish effective cerebral blood flow. The arrest time (AT) and the cardiopulmonary resuscitation (CPR) time to effective cardiac function represent a continuum from absence of cerebral blood flow to effective circulation, and together represent the total duration of ineffective cerebral blood flow. Short AT is compatible with good outcomes even after longer periods of CPR, whereas increasing lengths of AT reduce the time window for successful CPR. If AT is less than 6 minutes, prognosis for recovery is related to CPR time; over half of patients on whom CPR is successful within 30 minutes make a good neurologic recovery. When CPR time is longer, prognosis for neurologic recovery drops significantly. If AT exceeds 6 minutes, the chances of good neurologic outcome decrease [22]. Unsuccessful CPR before arrival at the emergency room predicts a poor prognosis [23]. Emergency crew–witnessed arrests, consciousness level on admission, and requirement for ventilation are independently useful to predict in-hospital outcome and mortality [24].

Magnetic resonance spectroscopy demonstrating elevated lactate and reduced *N*-acetyl acetate peaks is associated with a poor prognosis [25,26].

Cerebrospinal fluid (CSF) lactate levels [27], neuron-specific enolase, and brain-type creatine kinase isoenzyme levels may have predictive value 24 hours after cardiac arrest. Patients with either CSF neuron-specific enolase more than 33 µg per L at 24 hours or cerebrospinal fluid brain-type creatine kinase isoenzyme more than 50 U per L at 48 to 72 hours usually die. Creatine phosphokinase levels above 205 U per L are uniformly associated with a fatal outcome. A potentially useful laboratory screening test when lumbar puncture is not feasible is the serum neuron-specific enolase level, which has a fair correlation with outcome [28–30]. Similarly, S-100 protein, an astroglial marker, is elevated in anoxic arrest. Values of more than 0.2 mmol per L on day 2 are associated with 100% mortality, whereas values below this are associated with an 89% survival [31].

After out-of-hospital cardiac arrest, the overall probability of awakening is roughly 50% [32,33]. Much of this depends on the duration of coma. In cases of cardiac arrest, complete recovery occurs in 80% of patients in whom the coma resolves within 24 hours [32,33]. Others have shown that 72 hours is the upper limit for recovery of brain function sufficient to permit some degree of speech [34].

TREATMENT

Treatment approaches for cardiac arrest and perioperative hypoxic encephalopathy are similar. Optimal therapy is directed at preventing the recurrence of hypoxia. To ensure that the oxygen-carrying capacity of the blood is restored, excess oxygen administration is suggested for several hours after anoxic events. There is strong evidence that mild or moderate hypothermia may improve outcome after cardiac arrest [35,36]. Blood pressure is maintained at normotensive or mildly elevated levels. Mean arterial pressure should be 90 to 110 mm Hg in patients who are usually normotensive. The partial pressure of oxygen should be more than 100 mm Hg. The partial pressure of carbon dioxide is kept at the patient's baseline (usually 40 mm Hg), unless there are active signs of cerebral herniation; if herniation is suspected, the patient should be hyperventilated. Mild hypovolemia and elevation of the head of the bed to 30 degrees reduce intracranial pressure. Vital signs, hematocrit, electrolytes, blood sugar, and serum osmolality should be maintained in the normal range [12]. In all cases, a head CT or MRI scan and complete metabolic studies should be obtained to exclude structural and other functional causes. When any uncertainties exist, a neurologist should be consulted.

Seizures occur in 25% of patients in anoxic coma [4]. They are treated with loading and then maintenance doses of fosphenytoin (Cerebyx) (loading dose, 15 to 20 mg phenytoin equivalents per kg, rate not to exceed 100 mg phenytoin equivalents per minute; maintenance dose, 5 mg phenytoin equivalents per kg per day). Alternatively, intravenous phenytoin can be used (loading dose, 18 to 20 mg per kg; rate, 50 mg per minute; maintenance dose, 5 mg per kg). Patients with cardiac conduction abnormalities need to be carefully monitored while being loaded with fosphenytoin or phenytoin. Phenobarbital is usually avoided because of its sedative effects. If necessary, loading doses in adults are up to 500 mg intravenously, and maintenance doses are 2 to 4 mg per kg per day [37]. Because status epilepticus or frequent untreated seizures can further damage the brain, an EEG should be obtained if there is any question of subclinical epileptiform activity [10]. Some postanoxic patients develop delayed intention myoclonus. This can be distinguished from seizure activity because the latter is accompanied by an epileptiform discharge on the EEG, whereas myoclonus is not. Intention myoclonus can be treated with valproic acid.

Steroids, mannitol, and glycerol are ineffective and result in elevated serum blood glucose, which increase production of lactic acid, possibly potentiating preexisting damage. High dose barbiturates or calcium channel blockers have not demonstrated any improvement in outcome [38,39].

If the patient awakens, mobilization is initiated early to minimize the risk of bedsores and deep venous thrombosis. An empiric 7 to 10 days of bed rest may minimize the chance of developing postanoxic encephalopathy in cases of carbon monoxide poisoning [2,3].

Induced hypothermia may be protective. A randomized, controlled trial assessed the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest. Of the 77 patients who were randomly assigned to treatment with hypothermia (core body temperature 33°C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia, 21 of the 43 patients treated with hypothermia (49%) survived and had a good outcome, discharged home or to rehabilitation as compared with 9 of the 34 treated with normothermia (26%; $p = 0.046$). The odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95% confidence interval, 1.47 to 18.76; $p = 0.011$). Hypothermia was associated with a nonsignificant lower cardiac index, higher systemic vascular resistance, and hyperglycemia. The narrow inclusion criteria resulted in an international recommendation to cool only a restricted group of primary cardiac arrest survivors. In a broader retrospective study the efficacy and safety of endovascular cooling in unselected survivors of cardiac arrest was assessed. Consecutive comatose cardiac arrest survivors were either cooled to 33°C with endovascular cooling for 24 hours or treated with standard post-resuscitation therapy. Patients in the endovascular cooling group had twofold increased odds of survival (67/97 patients versus 466/941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; $p < 0.001$). After adjustment for baseline imbalances, the odds ratio was 1.96 (95% CI, 1.19 to 3.23; $p = 0.008$). Bayesian analysis revealed odds ratios of 1.61 (95% credible interval, 1.06 to 2.44). In the endovascular cooling group, 51/97 patients (53%) survived with good outcome as compared with 320/941 (34%) in the control group (odds ratio 2.15, 95% CI, 1.38 to 3.35; $p = 0.0003$; adjusted odds ratio 2.56, 1.57 to 4.17). There was no difference in the rate of complications except for bradycardia. The investigators concluded that endovascular cooling improved survival when compared with standard treatment in comatose adult survivors of cardiac arrest [40].

CONCLUSION

The effects of oxygen deprivation depend on many factors; the degree and duration of hypoxia are the most important. In cases of cardiac arrest, brain damage is proportional to the amount of time without perfusion. The patient's age, underlying medical conditions, infection, and other metabolic imbalances also play a role in the body's ability to withstand oxygen deprivation.

Treatment strategies for the acute phase focus on supportive care. Elevation of the head of the bed, maintaining a relatively hypovolemic state, and avoidance of hypotension may be of benefit. A vigorous search should be made for concurrent metabolic abnormalities. Induced hypothermia improves outcome; administration of steroids, osmotic agents, neuroprotective agents, and prophylactic anticonvulsants are ineffective measures and may worsen the prognosis.

Prognosis is best determined by the early return of brainstem and cranial nerve function. Absence of brainstem functions 72 hours after the event is associated with irreversible coma [11]. Other poor prognostic signs include a brainstem auditory evoked response showing no cortical waves 8 hours after the arrest and a CT scan demonstrating diffuse edema, loss of gray–white matter distinction, or watershed infarcts. The overall functional recovery rate is approximately 13%. If a patient has not regained consciousness by 6 hours after the onset of coma, the chance of survival for 1 year is 10%, and many of these survivors remain in a vegetative state.

Data from recent studies of out-of-hospital cardiac arrest patients treated by induced hypothermia to 32°C suggest a better prognosis (survival increased threefold and neurological recovery almost 4.5 fold compared to patients who did not undergo hypothermia.) This better outcome was limited to patients with a primary cardiac arrest who had initiation of successful CPR within 15 minutes and had a stable circulation within 60 minutes. Patients with significant pretreatment hypothermia, bleeding disorders, terminal or other serious comorbid conditions and unstable circulation after CPR were excluded. If one takes into account the retrospective nature of this study, the results are at best limited to the above population and can be considered hypothesis-generating data for future trials.

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CHAPTER 172 ■ STATUS EPILEPTICUS

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DEFINITION AND CLASSIFICATION

Status epilepticus (SE) was originally defined as seizures lasting longer than 30 minutes, or 30 minutes of recurrent seizures without return to baseline neurologic status between events [1]. This has been largely replaced by an operational definition of SE, which is a 5-minute duration of continued seizure activity, or two or more seizures between which there is incomplete recovery. SE is considered to be a condition in which there is "a failure of the 'normal' factors that serve to terminate a typical generalized tonic-clonic seizure" [2,3]. This approach is more clinically appropriate and promotes early treatment with antiepileptic medication. SE is usually divided into: (a) convulsive SE, in which the patient does not regain consciousness between repeated generalized tonic-clonic attacks; (b) simple partial SE, characterized by continuous or repetitive focal seizures without loss of consciousness [4]; and (c) nonconvulsive SE (NCSE), such as absence or complex partial SE, characterized by a prolonged confusional state of 30 minutes or longer. NCSE is also used to describe continued seizure activity in patients who have few or no clinical signs other than coma.

Convulsive Status Epilepticus

Most generalized tonic-clonic SE consists of partial seizures that have secondarily generalized; primary generalized SE is less common [5]. Most patients do not convulse continuously. Instead, seizures of a few minutes' duration may be followed by a prolonged period of unconsciousness that leads to the next seizure. During convulsive SE, massive autonomic discharge occurs with tachycardia and hypertension. Corneal and pupillary reflexes are lost and plantar reflexes may be extensor. As SE continues, the motor manifestations may evolve into more subtle activity such as low-amplitude focal twitching, nystagmus, eye deviation, or recurrent pupillary hippus. This is sometimes called *subtle generalized SE* [4]. SE may also present in this more subtle form, without initial convulsive activity, in patients who are very encephalopathic; electroencephalography (EEG) is required to confirm the diagnosis. Myoclonic SE is often classified as a form of convulsive SE; it can occur in children with chronic epilepsy and mental retardation. It is characterized by repetitive, asynchronous myoclonus with variable clouding of consciousness and may evolve into generalized tonic-clonic SE. In adults, the myoclonic syndromes that occur are usually secondary to toxic or metabolic encephalopathies, most commonly severe cerebral anoxia [6]. The patients are usually comatose, and the prognosis is poor. In both forms of myoclonic SE, the EEG shows repetitive generalized epileptiform discharges.

Simple Partial Status Epilepticus

Simple partial status epilepticus is the second most common form of SE, after generalized tonic-clonic SE [4]. In partial motor SE, focal clonic or tonic-clonic activity is localized to the face or an extremity. This activity may spread, corresponding to the somatotopic organization of the motor cortex, known as a Jacksonian march. Alternatively, the partial motor seizures may be multifocal, in this case often precipitated by metabolic disorders, such as hyperglycemia with a hyperosmolar nonketotic state [7]. *Epilepsia partialis continua* refers to a form of partial motor SE characterized by continuous, highly localized seizures that do not secondarily generalize and in which consciousness is maintained.

Nonconvulsive Status Epilepticus

NCSE is an under-recognized cause of coma. In a recent study, NCSE was documented in 8% of all comatose patients, without signs of seizure activity [8]. In additional studies, 31% to 37% of patients with unexplained altered mental status in intensive care units were in NCSE. NCSE is more likely to occur in the setting of acute medical problems, both systemic and neurologic [8–10].

Nonconvulsive SE includes absence and complex partial SE [4]. Clinically, both absence and complex partial SE present with a prolonged period of altered behavior and can masquerade as a psychiatric fugue state. Absence SE involves a variable level of altered consciousness, which may be accompanied by subtle myoclonic movements of the face, eye blinking, and occasional automatisms of the face and hands. The EEG is diagnostic, revealing continuous or discontinuous generalized spike and slow-wave activity. Complex partial SE involves either a series of complex partial seizures with staring, unresponsiveness, and motor automatisms, separated by a confusional state, or a more prolonged state of partial responsiveness and semipurposeful automatisms. In both of these forms of SE, the patient is partially or totally amnestic for the episode.

ETIOLOGY

Some of the major underlying etiologies and precipitants of SE are shown in Table 172.1. Precipitants are factors that provoke SE where it otherwise would not have occurred, but they are not the underlying cause of the seizure disorder. Symptomatic SE, defined as SE resulting from an acute or chronic neurologic or metabolic insult, is typically more common than idiopathic SE (presumed genetic etiology for the seizures in an otherwise neurologically normal person) [5]. In most series, at least two-thirds of cases of SE are symptomatic. In adults, a major cause of SE is stroke, comprising more than 25% of the cases in one series [5]. Decreasing antiepileptic drugs was also a significant cause of SE in this same series, occurring in approximately 20% of the cases. Other major causes include alcohol withdrawal, anoxia, metabolic disease, viral encephalitis including Epstein–Barr virus or herpes simplex virus, HIV infection, and drug abuse [11,12]. The acute insults can cause SE in patients with or without epilepsy. Children younger than 1 year and adults older than 60 years represent the populations most at risk for developing SE [5].

TABLE 172.1

ETIOLOGIES AND PRECIPITANTS OF STATUS EPILEPTICUS

- Etiologies
  - Structural brain lesion
    - Brain trauma
    - Brain tumors
    - Strokes
    - Hemorrhage
  - Central nervous system infections
    - Encephalitis
    - Meningitis
  - Toxic
    - Drugs (e.g., theophylline, lidocaine, penicillin)
    - Withdrawal states (e.g., alcohol, barbiturate)
  - Metabolic
    - Hypocalcemia
    - Hypomagnesemia
    - Hypoglycemia, hyperglycemia
    - Hyponatremia
    - Hyperosmolar state
    - Anoxia
    - Uremia
- Precipitants
  - Changes in anticonvulsant blood levels
    - Errors in medication
    - Change in drug regimens
    - Altered drug absorption
    - Noncompliance
  - Intercurrent infection
    - Fever (e.g., upper respiratory or gastrointestinal infections)
  - Alcohol withdrawal

PROGNOSIS AND SEQUELAE OF STATUS EPILEPTICUS

Mortality in SE depends on the specific etiology, duration of the episode, and the age of the patient [13]. The acute insult triggering SE is one of the most important factors influencing mortality. Among the etiologic groups, anoxia has been associated with the highest mortality rate, followed by hemorrhage, tumor, metabolic disorders, and systemic infection. Alcohol withdrawal and antiepileptic drug discontinuation have been associated with a low mortality rate. Patients with idiopathic SE have a low mortality rate. The duration of SE strongly affects the ultimate prognosis. In one study, patients with seizure duration of longer than 60 minutes had a mortality of 32.0%, whereas patients with seizure duration of shorter than 60 minutes had a mortality of 2.7% [13]. Age is significantly associated with mortality, with patients above the age of 70 having a dramatically greater mortality [5,13,14]. Despite improved medical care, convulsive SE still has an overall mortality rate in the range of 7% to 25% [5,13–15]. The mortality of complex partial SE was 18% in one study [16]. Other adverse outcomes include intellectual deterioration, permanent neurologic deficits, and chronic epilepsy.

SE itself can produce profound neuronal damage. Neuropathologic studies of the brains of children and adults who died shortly after SE reveal ischemic neuronal changes in the hippocampus, middle layers of the cerebral cortex, cerebellum (Purkinje cells), basal ganglia, thalamus, and hypothalamus [17]. These changes mimic those of severe hypoxia or hypoglycemia. The degree of hyperthermia during an episode of SE has also been shown to correlate closely with the degree of central nervous system (CNS) damage [18].

The perpetuation of SE is most likely caused by an imbalance between excitotoxic (primarily mediated by glutamate) and inhibitory (primarily mediated by γ-aminobutyric acid [GABA]) mechanisms [15,16]. This can be related to downregulation in GABA receptors or excitotoxic mechanisms involving glutamate receptors—both NMDA(*N*-methyl-d-aspartate) and non-NMDA receptors [3,15,19]. Calcium influx during excitation appears to be a critical component of neuronal injury and cell death, with activation of proteases and lipases leading to degradation of intracellular elements [19].

Abnormal neuronal activity alone can cause permanent neurologic injury. This is supported by the observation that patients with complex partial or partial motor SE who do not have concomitant hypotension, hypoxia, or hyperpyrexia can still have subsequent neurologic injury in the region of the brain associated with the seizure. Chronic memory impairment may follow complex partial SE [20], and focal neuronal necrosis (and edema) in the region of the brain involved with seizure activity has been found after partial motor status [21,22]. Focal magnetic resonance imaging (MRI) changes can be seen after prolonged epileptic activity, particularly on diffusion-weighted and perfusion MRI [23].

The natural history of NCSE is not well defined, especially mortality and morbidity. This is partly due to methodological issues, such as the lack of a uniform accurate definition of NCSE, and not assigning appropriate significance to the underlying etiology, mental status changes, and associated complications [24–26]. Kaplan [27,28] reviewed the prognosis of NCSE and suggested that prognosis depends not only on detailed assessment of NCSE type, but also on level of consciousness. In another study designed specifically to determine the rate of morbidity and mortality, mortality was associated with an acute medical cause as the underlying etiology, severe mental status impairment, and development of acute complications, but not the type of EEG changes [10].

SYSTEMIC COMPLICATIONS

If convulsive SE is not terminated promptly, secondary metabolic and medical complications occur (Table 172.2). Cardiac arrhythmias occur due to autonomic overactivity, acidosis, and hyperkalemia. This can be further complicated by shock due to lactic acidosis or by pharmacologic intervention for the status itself. Respiratory dysfunction may be caused by mechanical impairment from tonic muscle contraction, disturbed respiratory center function, massive autonomic discharge producing increased bronchial constriction and secretions, aspiration pneumonia, and neurogenic pulmonary edema. Neurogenic pulmonary edema results from ictal increases in pulmonary circulation with transcapillary fluid flux [17]. Renal impairment may occur from a combination of rhabdomyolysis with myoglobinuria and hypotension with poor renal perfusion. Hyperthermia can result from excessive muscle activity and hypothalamic dysfunction; alternatively, it may be due to an underlying infection that is responsible for the initiation of SE. The distinction of hyperthermia from an infection or from SE itself can be complicated by the peripheral leukocytosis [17] that occurs with status epilepticus due to demargination. This can result in a white blood cell count in the range of 12,700 to 28,000 cells per mm^3. The differential may be normal or may show lymphocytic or polymorphonuclear predominance, but band forms are rarely present. In addition, a mild cerebrospinal fluid (CSF) pleocytosis can occur with SE [17]. The maximum cell count is usually less than 80 cells per mm^3, with an initial polymorphonuclear predominance that reverts to a lymphocytic predominance as the pleocytosis resolves over a

TABLE 172.2

MEDICAL COMPLICATIONS OF STATUS EPILEPTICUS

	Early	Late (after 30 min)
Cardiovascular system	Tachycardia Hypertension	Bradycardia Hypotension Cardiac arrest Shock
Respiratory system	Tachypnea Apnea with carbon dioxide retention	Apnea Cheyne–Stokes Aspiration pneumonia Neurogenic pulmonary edema
Renal system	—	Uremia Acute tubular necrosis Myoglobinuria
Autonomic nervous system	Mydriasis Salivary and tracheobronchial hypersecretion Excessive sweating Bronchial constriction	Hyperpyrexia
Metabolic	Lactic acidosis Hyperglycemia Hyperkalemia	Lactic acidosis Hypoglycemia Liver failure Elevated prolactin

few days. Mild transient elevations in CSF protein may also occur. However, lowering of the CSF glucose level does not occur, and reduced CSF glucose immediately suggests an underlying bacterial or fungal infection.

Increased lactate production from maximally exercised muscles results in metabolic acidosis within minutes after the start of SE. There is a variable respiratory contribution to the acidosis from carbon dioxide retention. The degree of acidosis does not correlate with the extent of neuropathologic damage [17]. After cessation of the seizure, lactate is rapidly metabolized, resulting in spontaneous resolution of the acidosis. Initially, hyperglycemia develops due to catecholamine and glucagon release; later, hypoglycemia occurs due to increased plasma insulin, increased cerebral glucose consumption, and excessive muscle activity.

INITIAL ASSESSMENT AND MEDICAL MANAGEMENT

SE is a medical emergency and must be treated immediately in a critical care setting. Pharmacologic intervention is more effective at an early stage of SE than after a delay [3,14,15,19,29,30]. Treatment must be fourfold: termination of seizures, prevention of recurrent seizures, identification of etiology, and treatment of complications. This discussion concentrates on generalized tonic-clonic SE, which is the most common form of status in adults and has the most harmful neurologic sequelae.

The initial step is to confirm the diagnosis. The patient must be carefully observed to be sure that generalized seizures are recurring without recovery of consciousness. A flurry of seizures separated by a normal level of consciousness does not constitute SE (although urgent treatment may still be required). In the intensive care unit, NCSE may present clinically with a change in mental status only. As mentioned earlier, in this setting NCSE appears to be greatly underdiagnosed. For diagnosis of NCSE, certain well-defined EEG criteria need to be met, including repetitive epileptiform activity at more than 3 per second, or repetitive epileptiform activity at less than 3 per second but with incrementing or decrementing onset for 10 seconds or more and/or clinical improvement after antiepileptic drug (AED) use. The EEG ictal episodes should be continuous or recurrent for more than 30 minutes without improvement in clinical state, or return to preictal EEG between seizures [27,28].

Once a diagnosis of SE is made, treatment must proceed rapidly but deliberately. For generalized SE, the initial assessment and treatment should begin within 5 to 10 minutes of the onset of seizure activity. Table 172.3 outlines a management protocol.

It is important to obtain as much history as possible within the first few minutes of assessment, including any history of a preexisting chronic seizure disorder and antiepileptic drug use, alcohol or drug abuse, or any recent neurologic insult. The examination should focus on signs of systemic illness (e.g., uremia, hepatic disease, and infection), illicit drug use, evidence of trauma, or focal neurologic abnormalities. After appropriate blood samples have been obtained, glucose administration is recommended. Hypoglycemia is a rare but easily reversible cause of SE and may result in irreversible CNS damage if left untreated. Because glucose administration may precipitate Wernicke–Korsakoff syndrome in some individuals with marginal nutrition, thiamine should also be given. Subsequent intravenous (IV) infusions should consist of saline solution, as some AEDs precipitate in glucose solutions. The patient must be assessed for other metabolic consequences of status. Hyperthermia should be treated and oxygenation must be maintained. The metabolic acidosis that occurs does not adversely affect neurologic outcome and does not need treatment with bicarbonate [14,31]. Blood pressure must be carefully monitored; the systemic hypertension and decreased cerebrovascular resistance of early SE provide adequate blood flow for the increased metabolic demand in the brain, but eventually hypotension may occur, making the brain vulnerable to inadequate perfusion. Pharmacologic intervention for the seizures can exacerbate any hypotension.

TABLE 172.3

MANAGEMENT GUIDELINES FOR GENERALIZED STATUS EPILEPTICUS IN ADULTS

0–9 min:
If diagnosis is uncertain, observe for: recurrence of generalized seizures without intervening recovery of consciousness; continuous seizure activity > 5 min.

ABCs
Establish airway; pulse ox; administer 02; cardiac monitor.
Establish IV access (NS or saline lock), bedside rapid glucose determination.
Labs: CBC/diff, electrolytes, BUN/Cr/Glu, anticonvulsant drug levels, tox screen, other labs as indicated by history/examination.
If hypoglycemic give glucose (D50) 50–100 mL and thiamine 100 mg IV.

5–30 min:
Lorazepam 0.1 mg/kg IV (< 2 mg/min), given 2 mg at a time (or diazepam 0.1–0.2 mg/kg, < 2 mg/min).
Phenytoin 20 mg/kg IV at ≤ 50 mg/min (fosphenytoin 150 mg PE[a]/min), slower rate in elderly or if hypotension or bradycardia develop. Draw blood for level 10 min after infusion complete.
Cardiac monitoring, frequent BPs, careful observation of respiratory status, oximetry.
EEG monitoring, if possible.
Consider additional 5 mg/kg boluses of phenytoin to a maximum dose 30 mg/kg if seizures persist.
Lorazepam as needed for seizure during phenytoin load.

31–60 min:
If seizures persist: phenobarbital 20 mg/kg IV load, ≤ 100 mg/min. Or: induce coma, as below.
Anticipate respiratory depression and need for intubation.
If neuromuscular blockade required for intubation: EEG monitoring indicated.

> 1 h:
For persistent status: induce coma. Intubate if not previously done.
Continuous EEG to monitor for seizures and level of anesthesia.
Pentobarbital 5 mg/kg IV load (give over 20 min); repeat as needed to produce burst-suppression pattern. EEG may need to be completely suppressed if seizure activity persists during the bursts. Maintenance infusion 0.5–10 mg/kg/h.

OR
Midazolam 0.2 mg/kg IV bolus, infusion 0.1–2.0 mg/kg/h (tolerance after 72 h);

OR
Propofol 3–5 mg/kg IV bolus, 1–15 mg/kg/h infusion
Monitor for hypotension, ileus. Continue maintenance doses of phenytoin and phenobarbital; maintain therapeutic levels.
Once burst-suppression pattern established, monitor EEG every 1–2 h. Review at least 5 min of EEG every hour. Adjust medication dose as needed.
Taper medication at 12 h. If seizures recur, resume infusion for 24 h, then taper again. Continue this process as necessary.

[a]Fosphenytoin dosing in "phenytoin equivalents" (PE).
BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood cell; Cr, creatine; EEG, electroencephalogram; Glu, glucose; IV, intravenous; NS, normal saline.

It is essential to determine whether a metabolic disorder is causing the SE; if this is the case, pharmacologic intervention for SE alone is not effective. Systemic and CNS infections must be excluded, and lumbar puncture is often necessary. A contrast-enhanced head CT scan can be useful after the patient has been medically stabilized and the SE has terminated. MRI is preferred for suspected small or subtle lesions but is often not practical in the emergent setting.

PHARMACOLOGIC MANAGEMENT

A variety of drugs are available to treat SE. It is important to understand the pharmacokinetics of these drugs to ensure effective use. Table 172.4 outlines some of these properties.

IV benzodiazepines are an appropriate initial treatment. The Veterans Affairs Status Epilepticus Cooperative Study Group trial suggested that phenobarbital is also effective as initial therapy, but phenytoin alone without a benzodiazepine may be less effective [29,32]. Diazepam and lorazepam are both effective in treating generalized SE [33], but lorazepam has a longer duration of action (2 to 24 hours), compared to diazepam (10 to 25 minutes) [34], and does not have extensive peripheral tissue uptake, unlike diazepam. Although lorazepam has slower CNS penetration than diazepam, the onset of action of less than 3 minutes is acceptable. For these reasons, lorazepam is the recommended first-line agent in status epilepticus. Both these drugs have significant and essentially the same cardiac, respiratory, and CNS depressant side effects [30]. Respiratory depression and apnea, which are potentiated by age and previous administration of sedative drugs, may occur abruptly with doses as small as 1 mg. Hypotension, which occasionally occurs, may be partially due to the propylene glycol solvent contained in the IV forms of diazepam and lorazepam.

If IV access is not available, rectal diazepam has been successful in achieving rapid therapeutic levels and effectively terminating prolonged generalized seizures. A commercially prepared diazepam rectal gel is available for this purpose [35]. Significant respiratory depression from rectal diazepam has not been reported [36]. Intramuscular (IM) administration is unsuitable for the treatment of status due to delayed peak levels [37]. Furthermore, the peak concentration after IM injection is much less than that after IV injection for both agents.

Phenytoin is usually given with benzodiazepines to control the SE and prevent recurrent seizures. A 20 mg per kg load is recommended, given at 50 mg per minute. If seizures continue,

TABLE 172.4

PROPERTIES OF DRUGS USED TO TREAT STATUS EPILEPTICUS

Drug	Route	Loading dose	Rate of administration	Time to enter brain	Time to peak brain concentration (min)	Minimum effective plasma concentration (μg/mL)	Side effects
Diazepam	IV, rectal	0.1–0.2 mg/kg, up to 20 mg	2 mg/min IV	< 10 s	8	0.2–0.8	Respiratory depression/apnea (may be abrupt); hypotension; sedation, especially in combination with barbiturates
Lorazepam	IV	0.1 mg/kg	2 mg/min	< 2–3 min	23	0.03–0.10	Same as diazepam; amnesia
Phenytoin	IV	20 mg/kg	50 mg/min	1–3 min	3–6	15–30	Hypotension and electrocardiogram changes during acute administration; sedation at high doses
Phenobarbital	IV	20 mg/kg	100 mg/min	3 min	5–15	10–40	Respiratory depression and sedation common with increasing doses, especially when benzodiazepines used; hypotension

IV, intravenous.

additional doses of up to another 10 mg per kg can be given. The serum level of phenytoin should be 15 to 30 μg per mL. IM administration should not be used because it results in precipitation at the injection site and has slow, erratic absorption. Hypotension, electrocardiogram changes, and respiratory depression can occur and may be due partly to the propylene glycol diluent [3]. Simultaneous cardiac monitoring should be performed, and slower infusion rates (25 mg per minute) should be considered in patients who are elderly or have a history of cardiac arrhythmias, compromised pulmonary function, or hypotension [38]. The most common adverse effect is hypotension, which is age related and much less common in patients younger than 40 years. Intravenous infusion of phenytoin carries a risk of medication extravasation into adjacent tissue. Tissue necrosis can rarely occur [39].

Fosphenytoin, a water-soluble prodrug of phenytoin, is rapidly converted enzymatically to phenytoin. Rapid and complete absorption occurs after IM administration [40,41]. Therapeutic phenytoin concentrations are attained in most patients within 10 minutes of rapid IV infusion (150 mg per minute) and within 30 minutes of slower IV infusion or IM injection [40,41]. Dosing for fosphenytoin is the same as for phenytoin, but needs to be given in "phenytoin equivalents." Cardiac monitoring is required during IV infusions of fosphenytoin. Maintenance doses of phenytoin or fosphenytoin should be started within 24 hours of the loading dose, with levels maintained in the high therapeutic range (15 to 25 μg per mL).

The antiepileptic effect of phenytoin or fosphenytoin is maximal within 10 minutes after the infusion is completed. SE persisting after this time is considered refractory SE (RSE). Treatment from this point on may vary. A loading dose of phenobarbital may be given, 10 mg per kg at a rate of 100 mg per minute, repeated as needed up to a total dose of 20 mg per kg. Target blood levels are 30 to 40 μg per mL. Respiratory depression is a major side effect, especially if benzodiazepines have been used. The response rate to a third-line agent such as phenobarbital may be very low [3], and because of this, some centers proceed at this point to a drug-induced coma rather than administering phenobarbital. For drug-induced coma, all patients must be intubated, as anesthetic doses of medication are required. Agents commonly used for RSE include pentobarbital, midazolam, and propofol [38]. All are extremely effective at suppressing clinical and electrographic seizures. Simultaneous EEG monitoring is mandatory during induction of coma. Phenobarbital is not used for this purpose, because it results in very prolonged coma. Pentobarbital is administered as a loading dose of 5 mg per kg, given slowly, and repeated as necessary with additional 5 mg per kg loads to stop electrographic seizure activity. The maintenance dose is 0.5 to 10 mg per kg per hour [3,30,38]. Cardiac depression is often produced, and careful hemodynamic monitoring is required. Vasopressors are frequently needed, and ileus is also common.

Treatment with midazolam is initiated with a 0.2 mg per kg IV bolus followed by an infusion of 0.1 to 2.0 mg per kg per hour [42,43]. Patients regain consciousness more rapidly after discontinuation of midazolam than with pentobarbital. The short elimination half-life of midazolam may be significantly prolonged in critically ill patients and can lead to accumulation of the drug [44]. Tolerance to the effects of midazolam also can develop after 36 to 48 hours, which can lead to escalating dose requirements. Because of this, if status is not terminated within 72 hours of midazolam treatment, changing to a pentobarbital infusion is recommended.

Propofol, a GABA agonist, has also been used as a potent antiepileptic agent. The loading dose is 3 to 5 mg per kg, with an infusion rate of 1 to 15 mg per kg per hour [30,45,46]. One significant disadvantage of this drug is the propofol infusion syndrome. This consists of profound hypotension, rhabdomyolysis, hyperlipidemia, cardiac arrhythmias, and metabolic acidosis. It has been described primarily in pediatric patients, and propofol is therefore not recommended for pediatric SE. Propofol has the advantage of rapid induction and elimination, but slow downward titration is important to avoid recurrent seizures [47].

There is relatively little prospective data to suggest that propofol, pentobarbital, or midazolam are dramatically different in efficacy for SE. Several studies seem to indicate that patients treated with pentobarbital have fewer treatment

failures and breakthrough seizures, but more frequent episodes of hypotension. There is no clear difference in mortality among the three agents [48].

The dose of pentobarbital, midazolam, or propofol must be sufficient to terminate any seizure activity seen on the EEG. In many cases, the goal is to produce a burst-suppression EEG pattern, characterized by a flat background punctuated by bursts of mixed-frequency activity. If the bursts contain electrographic seizure activity, the coma should be deepened, at times to virtual electrocerebral silence. It is unclear if the coma needs to be deepened if only periodic sharp activity is seen on EEG. Further studies are needed to clarify fully what the appropriate EEG endpoint should be. During this time of drug-induced coma, maintenance doses of phenytoin and phenobarbital need to be continued and the serum levels kept in therapeutic range. Recently, propylene glycol toxicity has been reported in patients treated with barbiturate coma for refractory status epilepticus. These patients can develop hypotension and hepatic and renal failure. Hemodialysis is an option in these cases [49].

There is some evidence to suggest that intravenous valproate could be an appropriate second-line therapy. Intravenous valproate is well tolerated, with few adverse effects [50,51]. A loading dose of 25 mg per kg and an infusion rate of 3 to 6 mg per kg per minute have been used [52]. Studies have shown that it can be effective [53,54]. Although these early data appear promising, the overall role of IV valproate in the treatment of SE remains to be defined.

NCSE must be treated quickly, although the urgency is not as great as for convulsive SE. Diazepam and lorazepam are both effective in treating complex partial, partial motor, and absence SE. The response to benzodiazepines may be helpful in confirming the diagnosis if it is in question. The patient should also be started on antiepileptic medication appropriate for long-term management, given as a loading dose if appropriate. Valproic acid is an ideal drug for absence SE and can be given intravenously. The recommended starting dose is 15 mg per kg per day. Complex partial and partial motor SE both respond to phenytoin and phenobarbital, although epilepsia partialis continua can be notoriously resistant to treatment. Newer antiepileptic medications such as topiramate may also be effective, but need to be given orally [55]. The drug of choice for myoclonic status is valproate, but phenytoin and phenobarbital are also effective.

CONCLUSION

Status epilepticus is a true medical emergency and needs to be treated promptly and definitively. In convulsive SE, lorazepam is the drug of choice for immediate, short-term termination of ongoing seizure activity. A phenytoin loading dose should be administered simultaneously with the lorazepam. Phenytoin is safe and effective, has a rapid onset of seizure control, and may be used for maintenance therapy. If these drugs are ineffective, phenobarbital may be added, and if status still persists, a drug-induced coma should be induced. Physicians should be familiar with a treatment protocol, as appropriate therapy greatly reduces morbidity and mortality.

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CHAPTER 173 ■ CEREBROVASCULAR DISEASE

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Cerebrovascular disease encompasses ischemic stroke from thrombosis or embolism, and hemorrhagic stroke including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage. Many patients require management in the intensive care unit (ICU) due to the severity of disease or for monitoring after acute thrombolytic therapy. This chapter reviews the basic concepts of pathogenesis, diagnosis, evaluation, and management for patients with ischemic cerebrovascular disease (ICVD) and ICH. Subarachnoid hemorrhage is discussed in Chapter 78.

ISCHEMIC CEREBROVASCULAR DISEASE

ICVD comprises 85% of all strokes and is the most common neurologic problem that leads to acute hospitalization. Admission to the ICU is indicated in patients with (a) impaired consciousness; (b) associated comorbid conditions, particularly myocardial infarction; (c) stroke after coronary artery bypass grafting; (d) symptomatic secondary hemorrhagic conversion with neurologic deterioration; (e) for the initial 24 hours after administration of intravenous (IV) recombinant tissue plasminogen activator (rt-PA); and (f) after intra-arterial thrombolysis, angioplasty, stenting, or thrombectomy.

Pathophysiology

To ensure accurate diagnosis and appropriate therapy, ICVD is categorized along three axes: degree of completeness, anatomic territory, and underlying mechanism.

Degree of Completeness

Three degrees of completeness can be recognized: transient ischemic attack (TIA), stroke-in-evolution, and completed stroke. A TIA is an episode of temporary focal cerebral dysfunction occurring on a vascular basis. It typically resolves within minutes but may last up to 24 hours. A new definition was proposed and accepted when it was recognized that a significant percentage of patients whose deficits last up to 24 hours have minor stroke, not TIA. The new definition states TIA to be an acute vascular neurological deficit that is reversible within 60 minutes with no evidence of infarction on CT or MRI. A stroke-in-evolution is a neurovascular event that worsens over several hours to several days. In a completed stroke, the deficit remains fixed for at least 24 hours in the carotid system and for up to 72 hours in the vertebral-basilar system.

Anatomic Territory

Two broad clinical anatomic categories of ICVD syndromes are recognized, based on division of the cerebrovascular supply into those areas supplied by the carotid system (anterior circulation) and those supplied by the vertebral-basilar system (posterior circulation).

Symptoms commonly encountered in carotid system disease include aphasia, monoparesis or hemiparesis, monoparesthesias or hemiparesthesias, binocular visual field disturbance (hemianopia), or monocular visual loss. Symptoms that may be seen in vertebral-basilar system disease include hemianopia, cortical blindness, diplopia, vertigo, dysarthria, ataxia, and limb paresis or paresthesias, frequently with ipsilateral involvement of cranial nerve functions, and contralateral body involvement. Loss of consciousness or isolated vertigo rarely occurs without other vertebral-basilar symptoms. Other isolated symptoms, such as diplopia, amnesia, dysarthria, and light-headedness, usually do not serve as a basis for the diagnosis of vertebral-basilar disease; however, association with other brainstem symptoms may support this diagnosis [1].

Underlying Mechanism

Acute ICVD can be categorized as *large vessel thrombosis*, *small vessel thrombosis*, *cardioembolism*, or *stroke of*

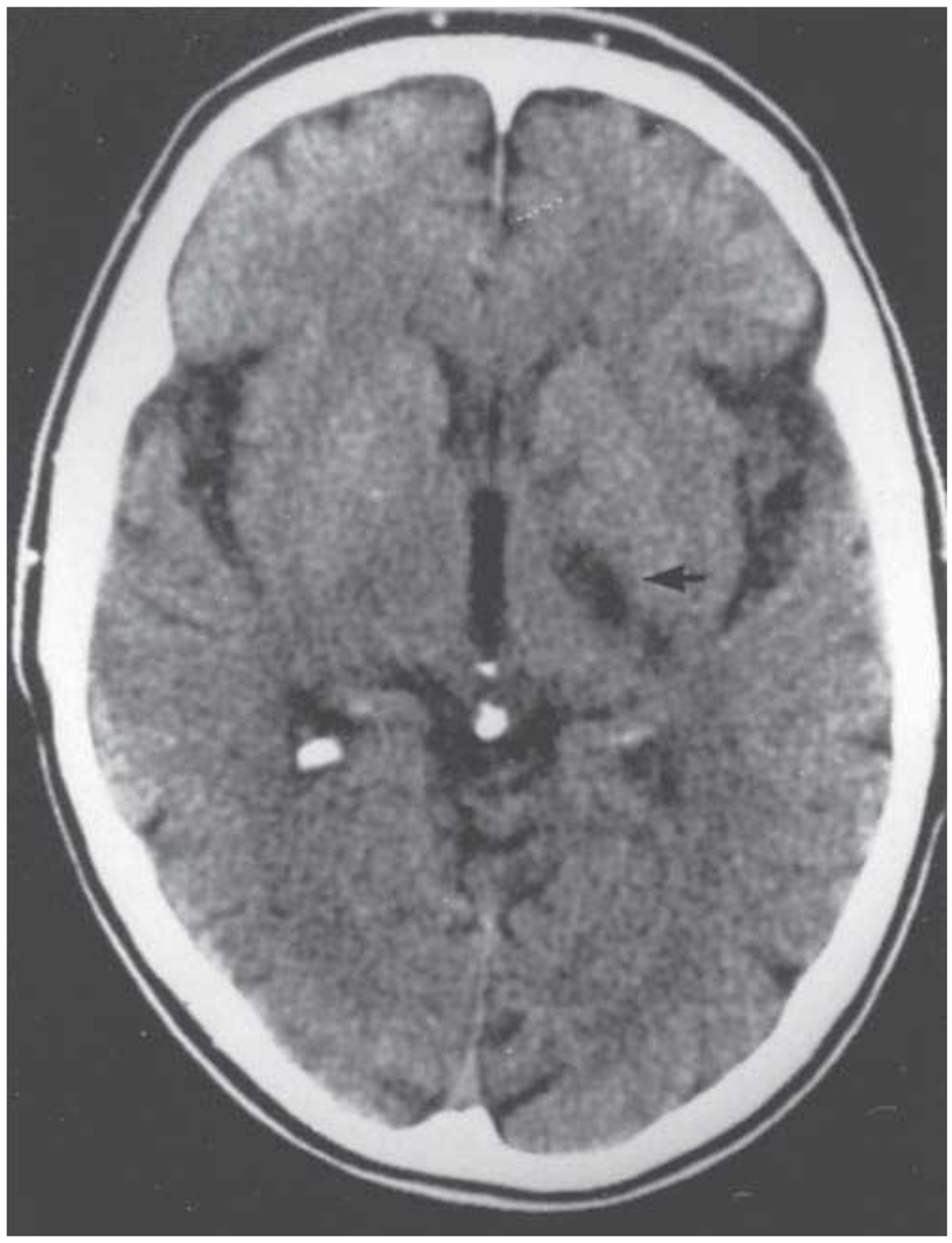

FIGURE 173.1. Lacunar infarct involving the left internal capsule seen on a computed tomography scan.

undetermined etiology. Large vessel atherothrombotic occlusion is due to atherosclerosis in the carotid or vertebral-basilar arteries and is a common cause of acute ICVD. The pattern and severity of the neurologic deficit depend on the arterial territory, completeness of occlusion, and collateral flow [1]. Small vessel occlusion occurs due to lipohyalinosis of the lenticulostriate arteries or basilar penetrators, and results in a small area of cerebral infarction called a *lacune* (Fig. 173.1). If a lacune is strategically placed in the internal capsule, thalamus, or basis pontis, substantial neurologic deficits occur. The most common lacunar syndromes are pure motor hemiparesis, pure sensory loss, ataxic hemiparesis, and dysarthria-clumsy hand syndrome [2].

The typical presentation of a cardioembolic stroke is with maximal deficit at onset, although a small minority may have a stuttering clinical course. Diagnosis may be difficult if the patient has coexistent large arterial lesions; as many as one third of patients with a cardiac embolic source have another potential explanation for their strokes [3]. The most common cardiac sources associated with cerebral embolic events are outlined in Table 173.1. Nonvalvular embolic source with atrial fibrillation is associated with a stroke risk of 4% to 5% per year, increasing with advancing age, the presence of paroxysmal/chronic atrial fibrillation, and an enlarged left atrium [4]. Transmyocardial infarction, atrial fibrillation, and mechanical valves are associated with a high risk, while the risk is lower in patients with bioprosthetic valves. Patent right-to-left cardiac shunts have been recognized by contrast echocardiography with increasing frequency in younger stroke patients. In the absence of a hypercoagulable state or atrial septal aneurysm, a patent foramen ovale (PFO) is not a significant risk factor for cardioembolic stroke, as up to 5% of the healthy population have a small PFO [5].

TABLE 173.1

CARDIAC SOURCES FOR CEREBRAL EMBOLI

Common
Nonvalvular atrial fibrillation
Acute anterior wall myocardial infarction
Ventricular aneurysms and dyskinetic segments
Rheumatic valvular disease
Prosthetic cardiac valves
Right-to-left shunts
Bacterial endocarditis
Less common
Mitral valve prolapse
Cardiomyopathy
Bicuspid aortic valve
Atrial myxoma
Nonbacterial endocarditis
Mitral annulus calcification
Idiopathic hypertrophic subaortic stenosis
Atrial septal aneurysm

Watershed infarction is due to globally diminished cerebral blood flow resulting from cardiac arrest or systemic hypotension, with focal infarction and deficits occurring in well-described patterns in the endarterial distribution between major vessels [6] (Fig. 173.2). In the carotid circulation, watershed infarcts occur between the distribution of the middle cerebral artery and either the anterior or posterior cerebral arteries. The usual anterior infarction causes contralateral weakness and sensory loss sparing the face; in posterior watershed infarcts, homonymous hemianopia with little or no weakness is most common. Quadriparesis, cortical blindness, or bilateral arm weakness (the "man-in-the-barrel" syndrome) may also be seen.

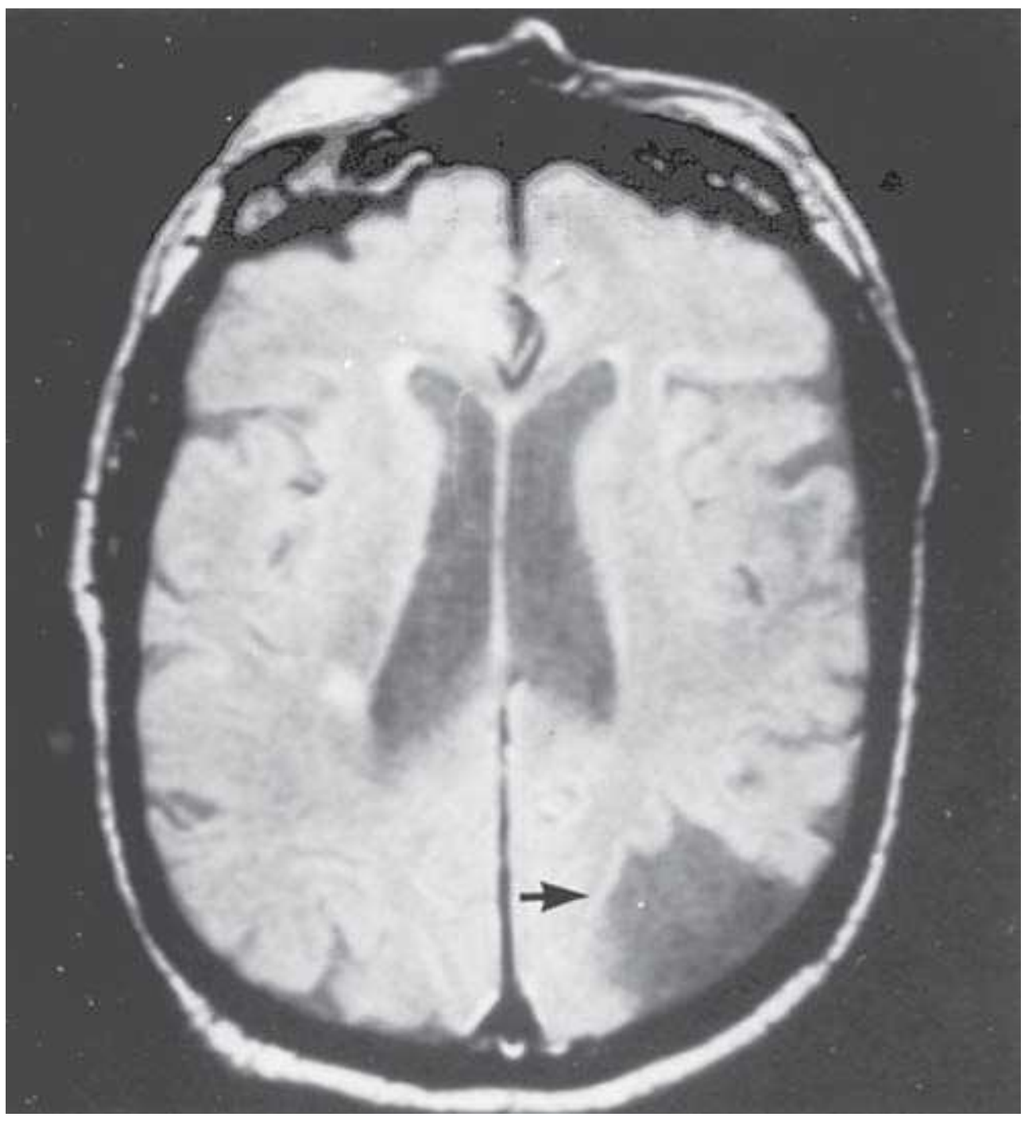

FIGURE 173.2. T1-weighted magnetic resonance imaging scan demonstrating a watershed infarction (*arrow*) in the border zone between the middle and posterior cerebral arteries.

Prognosis

The eventual prognosis of a completed stroke in either the carotid or vertebral-basilar distribution cannot be predicted with certainty during the initial phase of the ictus. The overall mortality varies from 3% to 20% in both vascular distributions [7]. Patients presenting with an altered level of consciousness, conjugate gaze paresis associated with contralateral dense hemiplegia, or decerebrate posturing have a poorer prognosis. However, functional outcome varies widely, with a favorable outcome observed in 20% to 70% of cases [8]. Lacunar syndromes are associated with very low 1-month mortality (approximately 1%) and good functional recovery in 75% to 80% of patients 1 to 3 months after stroke. The clinical course varies: One third of patients with large-artery atherothrombotic strokes have a progressive or fluctuating course, whereas less than one fifth of patients with cardioembolic disease follow a similar pattern [9]. More than 40% of patients with vertebral-basilar symptoms attributable to large-artery thrombosis have a progressive course.

Differential Diagnosis

The history and neurologic examination along with brain imaging enable the physician to differentiate among the major subtypes of ICVD: degree of completeness, territory involved, and ischemic mechanism. It is especially important to differentiate ICVD patients from those with primary ICH. Patients with cerebral hemorrhage typically have a progressive course, with evolution of symptoms over hours [10]. With recent improvement in imaging techniques (spiral computed tomography [CT], magnetic resonance imaging [MRI]), symptoms considered classic for ICH such as early obtundation, coma, seizures, headache, and vomiting are now known to be less reliable in making that diagnosis, since a similar presentation can be seen with ischemic stroke. Urgent imaging should remain the goal in all stroke patients presenting early within the first 3 hours of stroke onset, or those demonstrating worsening neurologic status. Conditions other than cerebrovascular events can occasionally cause acute focal neurologic deficits and must be considered. Primary or metastatic brain tumors with hemorrhage into the tumor may resemble a stroke (Fig. 173.3). Subdural hematomas may rarely present with acute focal neurologic deficits and must be considered in elderly patients, even without a history of head trauma. Patients with migraine headaches sometimes develop focal neurologic symptoms either before or during the early phase of the headache. Rarely, these deficits may occur in the absence of a headache (acephalgic migraine) or may persist (migrainous infarction). Patients with focal seizures may develop sensory, motor, and aphasic symptoms that can mimic ICVD, although they are usually stereotyped and transient. Occasionally, focal neurologic deficits may follow seizures and persist for 24 hours or longer (Todd's paralysis). In these cases, MR angiogram (MRA) or CT angiogram (CTA) can demonstrate arterial occlusion, making it more likely to be a stroke than Todd's paralysis. An important, uncommon, and reversible cause of acute neurological deficits is hypoglycemia, which should always be looked for before any aggressive treatment is initiated for a presumed ischemic stroke. Similarly in young patients or patients with a psychiatric history, objective neurological signs or corroborative radiological evidence must be established to avoid treating a functional paralysis with relatively aggressive therapy. Finally, worsening of an old deficit should prompt a metabolic/infectious evaluation, because the damaged cortex may act as a *locus minoris resistentiae*, with focal clinical worsening of a chronic deficit.

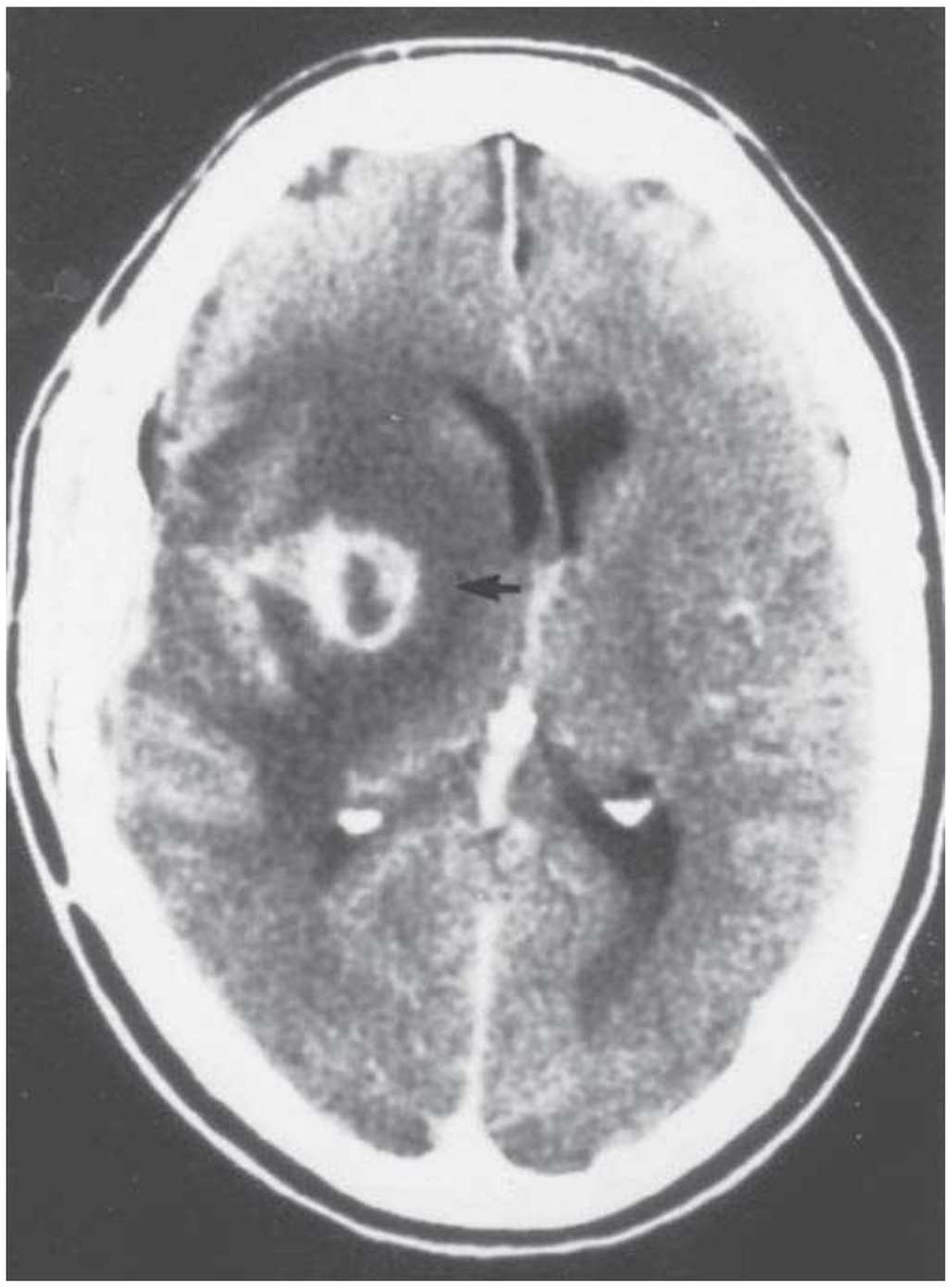

FIGURE 173.3. Malignant glioma with associated edema on a computed tomography scan in a patient who abruptly developed a pure motor deficit. The arrow points to the lacunar infarct.

Laboratory and Radiologic Evaluation

A comprehensive workup to determine stroke subtype, severity, and identification of possible multiple risk factors is important to determine effective treatment options. Early imaging in most ICVD patients helps in the differential diagnosis and is key in protocols for therapeutic intervention with rt-PA. Both CT and MRI scans are reliable and sensitive means of differentiating between ICVD, hemorrhage, and other mass lesions. MRI scans are more sensitive than CT scans for the identification of brain tumors, subarachnoid hemorrhage, and subdural hematomas, and MRI can identify ischemic infarction at an earlier stage (within 4 to 24 hours). MRI is probably more sensitive than CT in detecting intracerebral hemorrhage [11]. Newer MRI techniques, such as diffusion-weighted imaging (DWI) and perfusion imaging (PI), have important bearings on acute stroke diagnosis and treatment [12]. With DWI, ischemic lesions can be seen within minutes of onset. PI identifies areas of reduced blood flow, whereas in most cases, DWI hyperintensity indicates an area of irreversible ischemic injury. If the PI deficit is greater than the DWI area (DWI–PI mismatch), it demonstrates an ischemic tissue that is potentially reversible (ischemic penumbra). Magnetic resonance angiography (MRA), especially contrast-enhanced MRA (CEMRA), approaches the sensitivity of a four-vessel conventional angiogram. CEMRA has the added advantage of visualization of the vertebrobasilar system and the intracranial circulation with minimal increase in scan acquisition time. Early restoration of blood flow may result in normalization of this region, a reduced volume of infarction, and better stroke outcome. This is the basis of

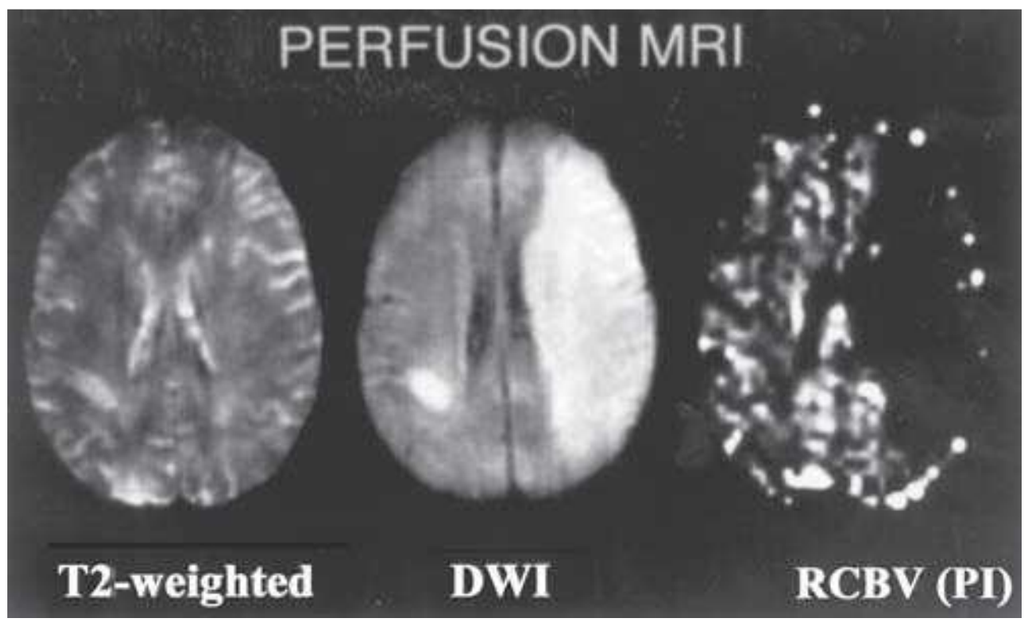

FIGURE 173.4. Magnetic resonance image of the brain with T2-weighted imaging, diffusion-weighted imaging (DWI), and perfusion imaging (PI) in a patient with acute ischemic stroke. Although T2 reveals very little change, there is a large DWI hyperintensity corresponding to a PI deficit (DWI-PI mismatch), demonstrating a completed infarct and a situation in which recombinant tissue plasminogen activator is not indicated. RCBV, regional cerebral blood volume.

thrombolytic therapy, and a persistent ischemic penumbra beyond 4.5 hours may be a reason to consider intra-arterial interventions [13,14] (Fig. 173.4).

An electrocardiogram should be obtained to assess possible underlying or concurrent cardiac rhythm or ischemic changes. Confusion may arise because T-wave, ST-segment, QRS complex changes, and rhythm disturbances may occur secondary to the cerebral ischemic event. Two-dimensional transthoracic, or transesophageal echocardiography, and telemetry/Holter monitoring should be done routinely because patients often have more than one potential underlying pathophysiology, and a cardiac structural or rhythm abnormality may change the treatment approach (Fig. 173.5). A transesophageal echocardiogram should especially be considered in younger patients, patients with an enlarged left atrium, and in cryptogenic stroke at all ages [14,15] (Fig. 173.6).

If an MRA has not been obtained to image the craniocervical vasculature, carotid artery ultrasound—a fast, reliable, and noninvasive technique—should be employed in suspected ischemic stroke of the carotid system as well as small vessel stroke, because of a high incidence of coexisting large vessel atherosclerotic stenosis. Transcranial Doppler ultrasound (TCD) can also provide information about the status of the

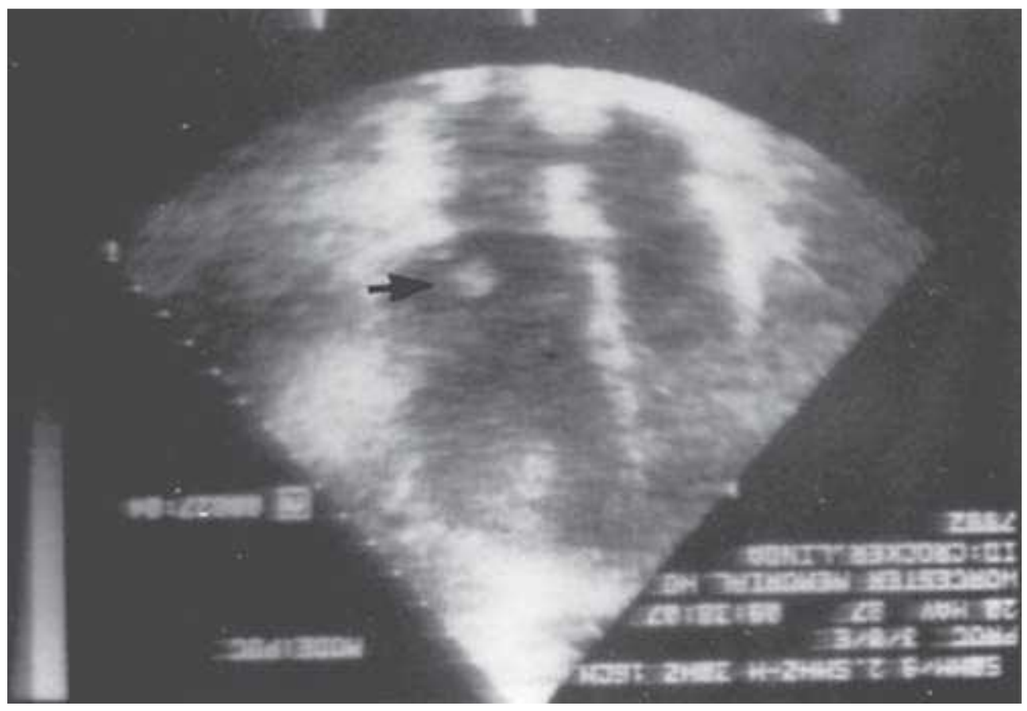

FIGURE 173.5. Echocardiogram in a patient with cardioembolic stroke, demonstrating a large thrombus (*arrow*) attached to the left mitral valve.

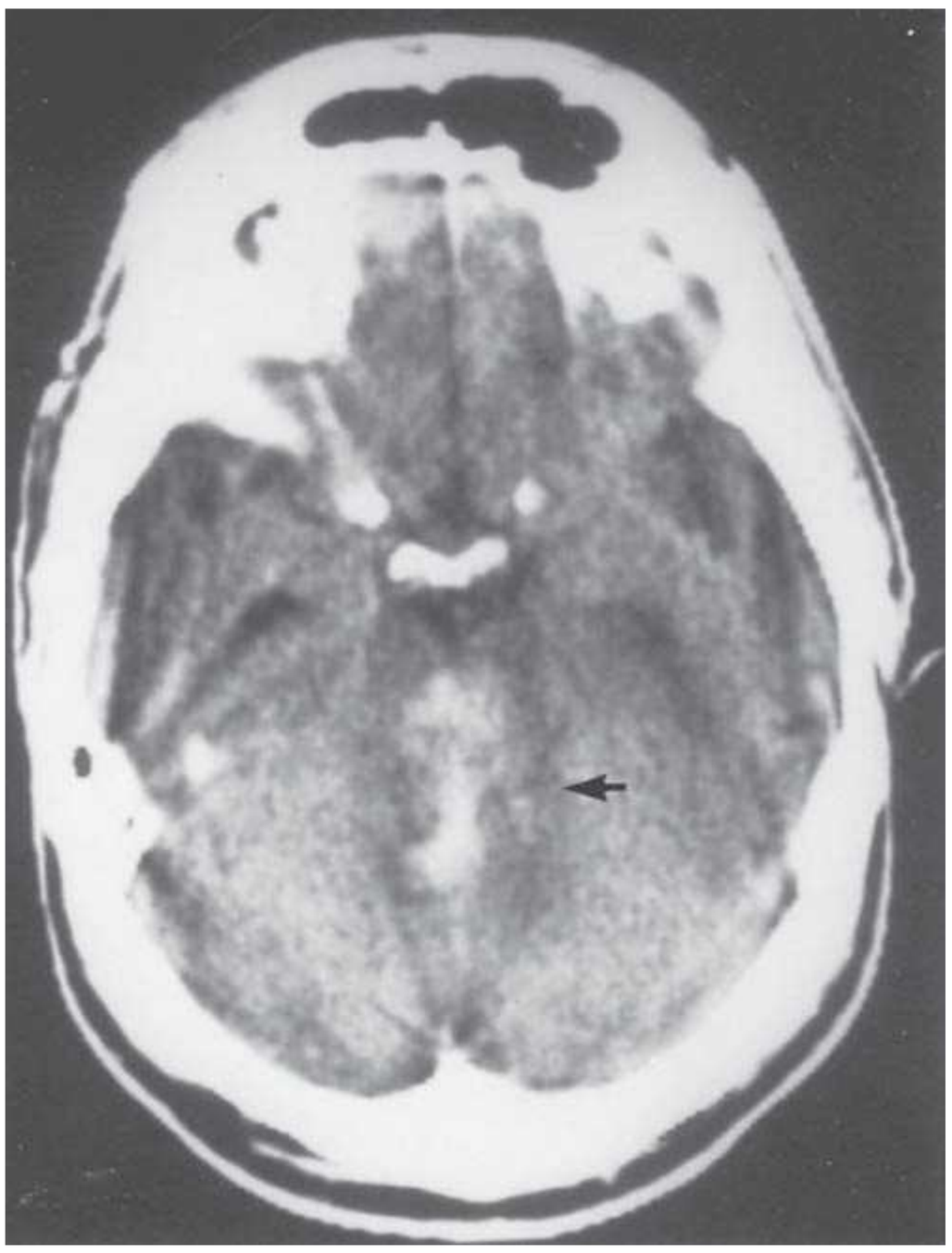

FIGURE 173.6. Midline cerebellar hemorrhage (*arrow*) seen on a computed tomography scan.

intracranial vessels, both in the carotid and vertebral-basilar arterial territories [16,17]. Advances in CT angiography (CTA) provide high-resolution vascular imaging as well as the ischemic penumbra with perfusion CT (CTP) studies. With a combination of noncontrast CT (NCCT), CTA, and CTP, it is possible to rule out hemorrhage, assess the extent of early signs of infarction, and determine the site of arterial occlusion and ischemic penumbra. The latter two studies are important in making decisions in acute stroke management (i.e., to proceed with intravenous or intra-arterial interventions). This CT based combination allows a more rapid triage compared to MRI, since every minute wasted before thrombolysis is initiated results in a progressive reduction of salvageable tissue.

Complete blood count, partial thromboplastin time (PTT), prothrombin time (PT), comprehensive blood chemistry, chest radiograph, erythrocyte sedimentation rate, syphilis serology, and urinalysis should be obtained on day 1. Of these, if thrombolytic therapy is being contemplated, the blood glucose, PTT, PT, and platelet count should be obtained immediately. Fasting lipid profile, homocysteine, and C-reactive protein should be obtained by day 2 in all cases. Other blood studies, including anticardiolipin antibodies, hypercoagulable workup (protein S, protein C, antithrombin 3, factor V Leiden, prothrombin-2 gene mutation), serum viscosity, serum protein electrophoresis, and fibrinogen, should be completed in younger patients and in patients with a history of cancer, recurrent deep vein thrombosis, or a family history suggestive of an autosomal-dominant pattern of stroke. A lumbar puncture should be performed only if meningitis is suspected, in suspected vasculitis of the nervous system, or when aneurysm rupture is a consideration, despite a negative result in a brain imaging study (NCCT or MRI). Electroencephalography may be helpful when associated seizure activity is suspected.

Treatment

The treatment of ICVD can be divided into four major categories: prevention, acute interventions, supportive therapy, and newer approaches.

Stroke Prevention

Stroke prevention has improved as risk factors have been identified and treatments developed [18]. The treatment of hypertension and smoking cessation are helpful in the prevention of stroke. Systolic blood pressure reduction by 5 to 10 mm Hg may reduce relative risk of ischemic stroke by 20% to 25%. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may offer additional protection against first or recurrent ischemic stroke. Patients with hyperglycemia should be aggressively treated to maintain euglycemic control (fasting blood glucose of less than 100 mg per dL). Use of HMG CoA reductase inhibitors (statins) reduces the risk of ischemic stroke by 25% to 30% in patients with underlying ischemic heart disease and possibly improves the outcome after AIS. The American College of Chest Physicians and American Stroke Association guidelines recommend starting all in-patients with hyperlipidemia (low-density lipoprotein [LDL] greater than 100 mg per dL) on statins. More recent trials of statins suggest that reducing LDL cholesterol to 70 mg per dL is safe and may have a plaque stabilization effect [19]. Patients with TIA have a substantial risk of stroke and should be completely investigated before discharge from the hospital. This is especially true for patients older than 60 years, those presenting with aphasia, motor deficits, or with associated diabetes. Patients with *symptomatic* carotid artery stenosis of greater than 70% benefit from carotid endarterectomy, provided the combined mortality and morbidity of the surgical procedure in the treating institution is less than 5.65% [20]. In nonsurgical TIA patients, antiplatelet therapy with aspirin, aspirin and extended-release dipyridamole (25/200 mg) twice daily, clopidogrel 75 mg once daily, or ticlopidine 250 mg twice daily is beneficial [21,22]. Indirect comparison of newer antiplatelet agents as compared to aspirin suggests that aspirin/extended-release dipyridamole (25/200 mg) (ERDP/ASA) twice daily is 23% more effective than aspirin alone, while clopidogrel offers no advantage over aspirin. However, the recently completed head-to-head comparative trial of clopidogrel vs ERDP/ASA failed to demonstrate a significant difference between the two medications. The combination of ERDP/ASA was associated with nonsignificantly fewer ischemic events, but with a greater number of intra- and extracerebral hemorrhages. On the other hand, there was a nonsignificant trend toward less congestive heart failure with this combination [23]. Atrial fibrillation with or without valvular heart disease is associated with a high stroke risk. Anticoagulation using warfarin reduces the absolute recurrent stroke relative risk by 8% in patients with nonvalvular atrial fibrillation. The annual risk of symptomatic hemorrhage is 1%, which can be minimized by keeping the international normalized ratio (INR) between 2 and 3 [15]. Ximelagatran, a thrombin inhibitor, in a head-to-head study with warfarin, failed to show noninferiority in reducing ischemic recurrent events and did not require INR monitoring, but the drug was not approved by the U.S. Food and Drug Administration (FDA) because of concerns of significant hepatic toxicity [24].

Supportive Therapy

Supportive therapy for ICVD patients should begin upon hospitalization. Elevated blood pressure should not be treated in the first 24 hours of an ischemic stroke unless malignant hypertension (> 220 over 120 mm Hg) is present or other end-organ failure becomes evident (e.g., congestive heart failure, renal failure). The blood pressure typically returns to baseline with bed rest; if it remains substantially elevated, it should be carefully lowered by no more than 20% of the mean arterial pressure. Subcutaneous heparin therapy should be considered for immobilized ICVD patients to reduce the risk of pulmonary emboli. Indwelling urinary catheters and excessive IV lines should be avoided, as they can promote infection. Elevated temperature should be lowered, as hyperthermia is clearly deleterious. Aspiration pneumonia can be avoided by delaying oral feedings until swallowing is well performed. Early mobilization and rehabilitation should be attempted.

Acute Treatment

Standard therapies in ICVD patients are directed at reversing the neurologic deficit and preventing progression. The National Institute of Neurological Disorders and Stroke (NINDS) trial demonstrated that patients treated with rt-PA within 3 hours of stroke onset had a 10% to 12% absolute greater chance of being free of disability or being left with minor disability at 3 months. The benefit was greatest for those treated within the first 90 minutes of stroke onset compared to those treated between 90 and 180 minutes. There was a tenfold greater incidence of ICH in treated patients as compared to placebo (6.4% vs. 0.6%). However, overall mortality at 3 months was comparable in the rt-PA and placebo groups. Predictors of ICH include large hemispheric infarcts, National Institutes of Health Stroke Scale (NIHSS) score greater than 23, and the presence of associated severe hypertension [25]. More recently, based on prospective trial (ECASS III) results it may be possible to extend the time window of intravenous rt-PA up to 4.5 hours. The absolute benefits, as expected, were less in this extended time window (ARR of 7%) and the results apply to mild and moderate stroke patients based on the NIHSS (median 8). While the study excluded older patients, those on anticoagulation (irrespective of the INR or PTT), and those with diabetes mellitus and stroke, the validity of these exclusions has not been substantiated and individual management should be decided for individuals based on the physician's judgment [26]. The total dose of 0.9 mg per kg is given as a 60-minute IV infusion, with 10% of the total dose given as an initial bolus. After rt-PA infusion, patients need to be admitted to the ICU. Blood pressure and neurologic status need to be carefully assessed at specified time periods. Systolic blood pressure above 185 mm or mean blood pressure over 130 mm are treated with intravenous labetalol/nicardipine or dose-titrated intravenous sodium nitroprusside. Neurologic worsening should prompt an urgent CT scan to look for possible hemorrhagic conversion of the infarct. Anticoagulants and antiplatelet agents are avoided in the first 24 hours. IV access and invasive procedures should be kept to a minimum in the first 24 hours after rt-PA administration. A recent trial of intra-arterial prourokinase, given within 6 hours of stroke onset, demonstrated improved stroke outcome in middle cerebral artery embolic infarctions [27].

Patients presenting beyond 4.5 hours who are not candidates for intravenous thrombolytic therapy may benefit from intra-arterial thrombolysis or mechanical embolectomy. The results of the Multi Mechanical Embolus Removal in Cerebral Ischemia (Multi MERCI) trial have limited application in the general stroke population because special equipment and trained interventionists are required for such interventions, and the outcomes in the extended time window of up to 8 hours did not demonstrate a result superior to intravenous rt-PA as in the NINDS trial. However, it did demonstrate that results comparable to the rt-PA outcomes were possible with delayed reperfusion [28]. This benefit still remains to be confirmed with the ongoing prospective, randomized trials (IMS 111) and MR and recanalization of stroke clots using embolectomy (MR RESCUE) where IV thrombolysis is followed by intra-arterial

interventions if no clinical improvement is demonstrated with the intravenous therapy. The results of a large retrospective analysis of intra-arterial interventions suggested that there was a significant 67% chance of achieving improved outcome (modified Rankin scale [MRS] ≤ 3) in the absence of a combination of older age, blood glucose > 150 mg per dL, and NIHSS > 18 [29].

Anticoagulation with heparin or low-molecular-weight heparin has been used traditionally without any proof of efficacy. However, heparin has been routinely considered in patients with a clear embolic source, with stroke-in-evolution to prevent progression, and with multiple TIAs to prevent stroke development. However, there is no evidence that supports the use of IV heparin anticoagulation to improve stroke outcome in progressive stroke. Furthermore, the risk of recurrent stroke is low (2% to 3%) in the first few weeks after an acute ischemic stroke (AIS) [30,31]. Cardioembolic stroke patients have a higher risk of recurrence (4.5% to 8.0%) within 2 weeks of the initial event, especially with associated intracardiac thrombi. Heparin therapy may reduce this risk and may be considered within 24 to 48 hours of the initial stroke [30]. Patients with large infarcts should not receive heparin, because they have a higher risk of bleeding into the area of infarction [19,30]. An alternative and safer approach is to begin warfarin as soon as the patient can safely swallow, leading to adequate anticoagulation within 5 to 7 days of stroke onset. The use of heparin therapy in stroke-in-evolution and in multiple TIAs is still under debate. If used, heparin should be initiated as a constant infusion without a bolus (although some stroke neurologists give a small initial bolus of 3,000 to 5,000 U), maintaining the PTT at 1.5 to 2.0 times control. Frequent PTT checks at 6-hour intervals and dose adjustment may reduce the frequency of serious intracranial and systemic hemorrhage [32].

Aspirin may reduce the risk of stroke recurrence after TIA or established stroke and is widely used for this indication [20]. Combined aspirin and extended-release dipyridamole therapy is twice as effective as aspirin alone in reducing stroke recurrence [21]. In aspirin-allergic patients, clopidogrel or ticlopidine can be used. The incidence of serious side effects is greater with ticlopidine, which may cause neutropenia and thrombotic thrombocytopenic purpura. Because thrombotic thrombocytopenic purpura has been reported with both drugs, weekly complete blood count and liver function tests should be done in the first 4 to 6 weeks of initiating therapy [33].

Cerebral edema in ICVD patients is maximal between 48 and 72 hours after onset, and corticosteroids are not effective in ICVD [34]. Osmotic diuretics, such as mannitol, are of uncertain value for cerebral edema associated with ICVD, but we consider using pulse doses (1.00 g per kg, then 0.25 g per kg every 6 hours) if massive edema begins to develop. Intracranial pressure (ICP) monitoring to guide therapy should also be considered. Controlled hyperventilation is perhaps the fastest and most effective temporizing measure to reduce cerebral edema, but its effects are transient and regional cerebral ischemia may worsen due to vasoconstriction. Timely decompressive hemicraniectomy reduces the risk of death by 50% (1 in 2 patients) and improves the outcome by 25% (1 in 4 patients). This has been validated in patients younger than 50 years, although there is no reason not to apply the procedure in older patients. Interestingly enough, the outcomes of this trial were independent of the side of infarction or the presence or absence of aphasia [34].

Recent Advances

Cerebral ischemic insult results in activation of the ischemic cascade. Under these circumstances, reduced reuptake and increased release of glutamate leads to activation of the *N*-methyl-D-aspartate receptors; reduced inhibition of γ-aminobutyric acid and glycine; and increased intracellular calcium influx, lipid peroxidation, and release of free radicals that hasten the process of cell death. Several neuroprotective agents blocking steps of the ischemic cascade have undergone animal studies and human trials. Although almost all reduce the infarct size in animal models of ischemic stroke, so far none have demonstrated any clinical efficacy [35–42]. There were several reasons why neuroprotective therapies have not proven effective in clinical trials. Serious side effects limited the effective doses of medications, the inclusion time to treatment may have been too long, and reperfusion was not established. To overcome these limitations, recent studies have begun to use combination therapies, combining rt-PA with neuroprotective drugs as well as combinations of two neuroprotective drugs with different sites of action [43]. Recently NXY-059, a free radical trapping agent, was reported to improve outcome of AIS, although the phase 3 trial results of the Stroke Acute Ischemic NXY-059 (SAINT) 11 trial conducted in the United States failed to confirm these findings [44]. Induced hypothermia may be useful in limiting damage from large hemispheric infarcts but at present remains an experimental procedure for ischemic stroke. Major problems limiting its use are the lack of availability of appropriate cooling devices, difficulty in obtaining rapid temperature reduction to target values, and complications during subsequent rewarming. Bihemispheric laser therapy of the brain showed promise as a method of improving outcome after ischemic stroke in phase 2 trials but failed to demonstrate efficacy in a subsequent phase 3 randomized trial [45].

Summary

Advances are being made in the treatment of ICVD. It is clear that successful therapy requires early intervention and close assessment for favorable responses and side effects, likely requiring an ICU setting initially. It is recognized that IV thrombolysis may not be effective in large vessel occlusions such as the internal carotid, proximal middle cerebral, and basilar arteries; however, randomized trials are underway to assess this. The current practice of giving full-dose IV rt-PA followed by intervention is widely practiced, but this is neither an FDA-approved therapy nor has it been shown to be beneficial in any case series. Perhaps ECASS 111 and MR RESCUE will provide the answers. Treatment of TIA has undergone a dramatic change since we recognized that the risk of a full-blown ischemic stroke is 10.5% after a cursory ER visit, and the risk can be reduced by 80% with acute in-patient management for 1 to 2 days, as demonstrated by the Oxfordshire study and the 2009 guidelines on management of TIA [46]. The recognition that acute high-dose statins reduce the risk of stroke and improve outcome irrespective of the low-density lipoprotein (LDL) levels is an important addendum to our management strategy within the acute period after an ischemic stroke. In the future, it is probable that a combination of treatments directed at the multiple metabolic and perfusion abnormalities associated with ICVD will be required [47]. Finally, stroke prevention is the most effective means of reducing the first or recurrent stroke. Aggressive use of statins in patients with either hyperlipidemia or elevated C-reactive proteins reduces the risk of progression of atherosclerotic small and large vessel disease and has a cardioprotective role.

INTRACEREBRAL HEMORRHAGE

Nontraumatic ICH occurs less frequently than ICVD but often requires management in the ICU. The majority of cases are due to spontaneous (primary) ICH or rupture of saccular

aneurysms and arteriovenous malformations. As the approach to these entities and their management differ considerably, they are discussed separately.

Primary ICH is defined as bleeding within the brain parenchyma without an underlying cause, such as neoplasm, vasculitis, bleeding disorder, prior embolic infarction, aneurysm, vascular malformation, or trauma. One-half of primary ICH cases result from longstanding hypertension. Due to the aggressive control of hypertension, the incidence of ICH has decreased since the mid-1960s. Nonetheless, ICH accounts for 4% to 11% of all stroke cases in the United States and 16% to 26% of all stroke-related deaths [47].

Pathophysiology

ICH is believed to be due to extravasation of arterial blood from ruptured microaneurysms along the walls of small intracerebral arterioles. Microaneurysms known as *Charcot–Bouchard or miliary aneurysms* tend to form on vessels at the usual sites of ICH and develop at sites of vascular branching where mechanical stress is maximal. The aneurysm wall lacks normal vascular histology and is composed mainly of connective tissue layers, which represent a weak point in the arterial system. The formation of these aneurysms is favored by the processes of lipohyalinosis and fibrinoid necrosis, which weaken the walls of arterioles, and are accelerated by chronic hypertension. Although Charcot–Bouchard aneurysms also appear in the normotensive aging brain, their frequency is notably increased in hypertensive patients. They are commonly observed along the lenticulostriate arteries, thalamoperforate arteries, and paramedian branches of the basilar artery. Although this distribution corresponds to the common sites of ICH, it is impossible to prove that these aneurysms are always the cause of bleeding, and the concept of arteriolar microdissection has been raised as an alternative explanation [48].

Continued extravasations of blood result in the formation of a hematoma with secondary accumulation of cerebral edema. The lesion may become massive enough to cause midline shift of cerebral structures followed by transtentorial herniation, which leads to secondary brainstem hemorrhages known as *Duret hemorrhages*. These linear lesions in the midbrain and upper pons are generally multiple and bilateral. Progression of this process results in brainstem dysfunction and death. Depending on the size and location of the ICH, intraventricular extension can occur and lead to the development of acute obstructive hydrocephalus or the later development of a chronic communicating hydrocephalus from impaired cerebrospinal fluid resorption. Some cases of thromboembolic stroke may be misclassified as ICH, because blood may extravasate and accumulate into large hematomas in areas of infarction. This secondary hemorrhage may be mislabeled if an early imaging study is not performed.

Clinical Manifestations

The clinical presentation of ICH is distinctive. In most cases, the onset is during the waking state when the patient is active; it is unusual for ICH to occur during sleep. The onset is abrupt, and the development of neurological deficits occurs progressively over minutes to hours. This contrasts with the fluctuating or stepwise progression of deficits commonly seen in atherothrombotic infarcts, and with the appearance of maximal deficits at onset in cardioembolic strokes. In addition, prior TIA is rare with ICH and relatively common with ischemic stroke. The average age of onset of ICH, 50 to 70 years, is younger than that of other types of stroke. Patients may report lateralized headache; vomiting is common and nuchal rigidity may be present. Seizures are seen more frequently at the onset of ICH (17%) than in ICVD and are more likely to occur if the bleeding involves the cerebral cortex [49]. When first seen by a physician, 44% to 72% of patients are comatose.

The clinical presentation of ICH is monophasic, with active bleeding usually lasting no longer than 2 hours. However, secondary bleeding and subsequent deterioration may occur. Subsequent clinical deterioration is due to the effects of cerebral edema [50]. It was recently suggested that thalamic hemorrhages may bleed further in patients whose hypertension is not adequately controlled [51].

Diagnosis

The diagnosis of ICH can be made by CT scan, which provides accurate information about the size and site of the hematoma as well as the midline shift, and development of cerebral edema. Typically, the hemorrhage is hyperdense on CT scan during the acute phase, although severe anemia or ongoing hemorrhage may make the appearance more iso- or hypodense. The appearance of blood on the MRI scan varies because signal intensity is related to the state of degradation of the hemoglobin. This state changes with time; therefore, MRI is not the study of choice for initial imaging of ICH. In summary, deoxyhemoglobin is found in the first 3 days after ICH and is not well visualized on T1-weighted images but appears as an area of reduced signal intensity on T2-weighted images. Days 3 to 10 after ICH, methemoglobin appears as increased signal intensity of T1-weighted images, but the intracellular portion has reduced signal intensity on T2-weighted images. In the chronic state, the ICH has broken down to hemosiderin, which is poorly visualized on T1-weighted images but appears as reduced signal intensity on T2-weighted images. Magnetic resonance or conventional angiography should be considered in selected cases if an underlying aneurysm or arteriovenous malformation is suspected.

Lumbar puncture is contraindicated in ICH because of the risk of herniation from mass effect. Testing on admission for ICH should include coagulation profile and platelet counts in all patients, as well as bleeding time, if the patient is on aspirin.

Differential Diagnosis

Although the majority of ICH is hypertensive in origin, other etiologies should always be considered. Secondary cerebral hemorrhage may occur after embolic infarction as the lodged embolus fragments and ischemic distal vessels may rupture on reperfusion. This is more common in patients with large embolic infarcts, in patients who are anticoagulated, and in patients with poorly controlled hypertension. ICH secondary to reperfusion may also occur after carotid endarterectomy.

ICH accounts for 0.5% to 1.5% of all bleeding events related to the use of oral anticoagulants. Oral anticoagulation increases the risk of ICH 8- to 11-fold, compared to unanticoagulated patients. Compared with patients with spontaneous ICH, there is a trend toward larger hematomas and a higher mortality rate in patients on anticoagulants [52]. Cerebellar hemorrhage is relatively common in anticoagulated patients, and mortality in these cases may be as high as 65%. Therefore, in anticoagulated patients the onset of focal neurological signs, even if slowly progressive, necessitates CT scan to rule out ICH [53].

The use of fibrinolytic therapy, such as rt-PA, for coronary artery occlusion has also been associated with ICH, especially when concomitant heparin therapy is used. These cases have shown a predilection for the subcortical white matter and lobar areas, generally having a poor prognosis [54]. Surprisingly, the

risk for ICH is slightly higher with rt-PA than with streptokinase [55].

ICH associated with the presence of primary or secondary brain tumors is infrequent, accounting for only 2% of all cases of ICH. Higher-grade malignancies, such as glioblastoma multiforme, are more likely to bleed. The presence of thin-walled vessels in areas of neovascularization is thought to be the underlying reason for these hemorrhages. Metastatic lesions with the tendency to bleed include bronchogenic carcinoma, melanoma, renal cell carcinoma, and choriocarcinoma. ICH is frequent in hematologic disorders such as leukemia and reflects both the underlying thrombocytopenia and disseminated intravascular coagulopathy. When disseminated intravascular coagulopathy is due to other organ failures, it can also lead to ICH.

Sympathomimetic drugs, such as methamphetamine, pseudoephedrine, and phenylpropanolamine, have caused ICH in the subcortical white matter. These agents are suspected of inducing a vasculitis. Cocaine, which blocks dopamine and norepinephrine reuptake, has been associated with ICH. Cocaine, especially crack cocaine, appears to incite cerebral vasospasm rather than a vasculitis. The secondary hypertension related to sympathetic stimulation may also cause ICH from any of these agents. This may explain the lack of abnormal angiographic findings in some of these cases [56,57], although recently cerebral vasospasm was demonstrated with magnetic resonance angiography after acute cocaine administration [58]. Acute elevation of blood pressure in otherwise normotensive people, such as that which may follow migraine, is postulated to result at times in ICH.

Specific Syndromes of Intracerebral Hemorrhage

ICH tends to occur in stereotyped locations. In order of descending frequency, these locations are the putamen (30% to 50%), subcortical white matter (15%), thalamus (10%), pons (10%), and cerebellum (10%) [59].

ICH in the putamen is caused by bleeding from a lenticulostriate vessel. Clinically it is manifested by development of flaccid hemiplegia, hemisensory disturbances of all primary modalities, homonymous hemianopia, paralysis of conjugate gaze to the side opposite the lesion, and early alteration in level of consciousness. Subcortical aphasia may occur when a putamen hemorrhage involves the dominant hemisphere, and a hemineglect syndrome when it is on the nondominant side.

Hemorrhages in the subcortical white matter (lobar hemorrhages) are being observed with increasing frequency, particularly in the elderly, and are less commonly related to hypertension than is ICH in other locations. The signs and symptoms depend on the location. Lobar ICH occurs at the gray-white junction and is, therefore, associated with a higher incidence of seizures and headache at onset; it most commonly occurs in the parietal and occipital lobes. Of all ICH locations, lobar hemorrhages have the lowest mortality (approximately 15%) and carry the best prognosis for a good functional recovery. Lobar ICH is frequently caused by cerebral amyloid angiopathy due to the deposition of amyloid in the walls of the small vessels of the cortex and leptomeninges, typically in the frontal and occipital lobes. The process generally spares vessels of the basal ganglia, deep white matter, brainstem, and cerebellum. The abnormal vessel walls take up Congo red stain, thus the alternative term *congophilic angiopathy*. Amyloid angiopathy weakens the walls of many arteries and may be associated with recurrent lobar ICH. Five to ten percent of cases of spontaneous ICH result from amyloid angiopathy, making it second to hypertension as an etiology for ICH [60].

Thalamic ICH is characterized by a unilateral sensorimotor deficit in which sensory findings predominate. A variety of eye signs occur: Parinaud's syndrome, forced disconjugate downgaze deviation medially on the side opposite the lesion, pseudoabducens paresis, up-gaze paralysis, and so forth. The most specific localizing sign is inferomedial disconjugate gaze paresis contralateral to the side of the lesion. A permanent skew deviation, with vertical separation of images, may leave the patient with persistent diplopia. Due to the location, thalamic ICH may rupture into the ventricular system.

Pontine ICH has the highest mortality. Quadriplegia, brainstem dysfunction, and small, unreactive pupils are seen at presentation and many patients rapidly develop coma. Bleeding typically arises from a paramedian branch of the basilar artery and almost always extends into the fourth ventricle. Cases of unilateral pontine ICH have a better outcome [61].

Cerebellar ICH most commonly involves the dentate nucleus (see Fig. 173.5). Alteration of consciousness is unusual at onset, but progressive deterioration with drowsiness typically occurs. The majority of patients initially manifest two of the following: (a) gait, truncal, or limb ataxia; (b) lower motor neuron facial paresis; and (c) an ipsilateral gaze palsy. Other common presenting signs and symptoms are headache, nausea, vomiting, vertigo, nystagmus, and limb ataxia [62]. Early surgical intervention is indicated for lesions larger than 3 cm or in smaller lesions with clinical progression, because cerebellar hemorrhage causes death in up to 60% of cases. Neurologic deterioration due to hemorrhage, causing obstructive hydrocephalus at the level of the fourth ventricle, is not uncommon. Surgical mortality is greatly reduced if the patient is still awake before operation; therefore, early intervention is indicated [62].

Approximately 3% of cases of ICH are primarily intraventricular in location. These events have minimal focal signs, but generally, there is loss of consciousness at onset. Hydrocephalus is a major complication [63].

Treatment

The acute medical management of ICH is aimed at correction of any predisposing systemic factors to prevent further clinical deterioration. Following ICH, there is a hematoma growth of 22% within the first 24 hours and hypertension is a major management problem in these cases. In response to the acute elevation of ICP caused by the hematoma, systemic blood pressure rises to maintain adequate cerebral perfusion pressure. This response, known as *Cushing's reflex*, serves to protect the brain against ischemia, but autoregulation of cerebral blood flow can be impaired after ICH or infarction. In patients with underlying chronic hypertension, the result may be excessively high blood pressure. The best management of this dilemma remains controversial. In chronic hypertension, the lower limit of cerebral autoregulation is shifted toward higher blood pressure; and acute lowering of systolic blood pressure is known to result in unfavorable decreases in cerebral perfusion pressure. Sustained hypertension in the acute phase of ICH, however, can lead to further bleeding or rapid accumulation of cerebral edema [59]. The recommended goal of systolic blood pressure in the acute phase of ICH is between 110 and 160 mm Hg [64]. Blood pressure should be lowered gently, and beta-blockers are the agents of choice. Alternatively, a calcium channel blocker such as intravenous nicardipine may be useful because it does not elevate ICP like other vasodilators [59].

If the hematoma and associated cerebral edema raise ICP, clinical deterioration typically occurs. Acutely, hyperventilation effectively lowers ICP, but only for a matter of hours. Hyperosmolar agents, such as mannitol, sorbitol, and glycerol, provide more sustained reductions in ICP. These drugs reduce the fluid content of the intact brain so that the cranial

cavity can accommodate cerebral edema. The osmotic diuresis induced by these agents can lead to dehydration, electrolyte imbalances, and pulmonary edema if the patient is not closely monitored. Treatment of ICH with steroids can be detrimental to overall outcome, so they are not routinely administered [65]. The value of ICP monitoring in these situations remains controversial [65]. Elevation of ICP due to hydrocephalus is treated with ventricular cerebrospinal fluid diversion.

Anticonvulsants are not routinely used in ICH. If seizures are not present at onset, patients are generally at low risk for developing seizures, but hemorrhage into the cortex, regardless of site of origin, predisposes to seizures. Subarachnoid or intraventricular extension of bleeding does not increase the risk of seizures. Seizures have been noted with hemorrhages in the caudate but not with putaminal or thalamic events. Although the incidence of chronic epilepsy from ICH is low (6.5% to 13.0%), any seizures usually begin within the first 2 years after the event [66]. Prophylaxis against peripheral venous thrombosis should be accomplished with pneumatic boots.

After the patient is acutely stabilized, angiography may be performed if there is no history of hypertension or the bleeding is in an atypical location. This is particularly important or pertinent for younger patients, in whom a larger percentage of cases of ICH are due to underlying vascular lesions, such as arteriovenous malformation or aneurysm. At present, surgery may be indicated for lobar ICH in which the patient continues to deteriorate, and for most cerebellar ICH. Emergency ventriculostomy to relieve hydrocephalus should be considered if this condition develops acutely. Surgical intervention for putaminal ICH remains controversial; it is inappropriate for thalamic and pontine hemorrhages.

The prognosis for ICH is worse for larger lesions. By location, pontine ICH has the highest mortality, followed by cerebellar and then basal ganglia lesions. Lobar ICH carries the most favorable outlook for survival and functional recovery [52]. Three factors that have accurately predicted 30-day survival in 92% of ICH patients reviewed are hemorrhage size, Glasgow Coma Scale score, and pulse pressure [46].

Summary and Advances

ICH can be neurologically devastating. Patients with ICH often require an ICU setting because of the severity of disease, particularly when it is complicated by markedly increased ICP. Evacuation of the hematoma was not found to be helpful in randomized trials [67]. However, subgroup analysis suggested a possible role of surgical evacuation in hematoma that are superficial and less than 1 cm from the cortex. A subsequent trial, STICH 2, is underway to address this issue. Recombinant factor VII showed promise in phase 2 trials in reducing hematoma growth and improving outcome but a randomized phase 3 trial did not show any significant improvement in outcome after intracerebral hemorrhage, even though the hematoma growth was reduced [68,69]. Off-label use in reversal of anticoagulation-based ICH is sometimes practiced but with uncertain outcomes.

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CHAPTER 174 ■ NEURO-ONCOLOGICAL PROBLEMS IN THE INTENSIVE CARE UNIT

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INTRODUCTION

Neuro-oncology encompasses the care of patients with neoplasms affecting the brain, spinal cord, and peripheral nervous system. These tumors may arise either within the nervous system itself or spread from systemic malignancies. Neuro-oncology patients may require care in an intensive care unit (ICU) at a number of different phases of their illnesses. Usually, postoperative patients with brain tumors are admitted to the ICU. Neuro-oncology patients are also admitted to the ICU if they suffer catastrophic or near catastrophic neurologic decline or if they are at high risk to suffer such a change. Lastly, neuro-oncology patients may also suffer from medical processes that require intensive care.

This chapter discusses the intensive care issues that may be encountered in neuro-oncology patients, either following their surgery or as complications of their diseases. These issues include elevated intracranial pressure (ICP), hydrocephalus, seizures, postoperative complications, spinal neoplastic disease, and medical systemic complications.

ELEVATED INTRACRANIAL PRESSURE

Elevated ICP frequently complicates the course of patients with cerebral neoplasms. Both primary and metastatic tumors in the brain can cause elevated ICP. Patients with aggressive brain

tumors often succumb as a consequence of uncontrollable elevations in ICP.

Pathophysiology

Normal intracranial pressure ranges between 5 and 15 cm H_2O. This pressure is generated by the volumes of the various components contained in the "closed box" of the skull. These components include brain parenchyma, cerebrospinal fluid (CSF), extracellular water, and blood in vascular spaces. A perturbation of any of these components can increase ICP. Any additional tissue not normally present in the brain, such as a primary or metastatic tumor, or a hemorrhage associated with a tumor, can also increase ICP. While the numerical value of the ICP cannot be ascertained by neurodiagnostic images, some of the perturbations are evident on either computed tomography (CT) scan or magnetic resonance imaging (MRI).

Brain tumors can affect each intracranial component. In addition to the volume of the neoplasm itself, cerebral neoplasms can produce vasogenic edema [1], secondary to increased permeability of blood vessels within or adjacent to the tumor, thereby increasing extracellular water [2,3]. Radiographically, this edema corresponds to hypodensity on CT or hyperintensity on T2-weighted MRI around the enhancing bulk of tumor. Tumor mass, or brain parenchyma displaced by tumor, may obstruct CSF pathways, causing hydrocephalus. Hydrocephalus will be discussed in further detail in the section "Hydrocephalus." Intravascular blood volume also can increase in patients with tumors as a result of hypoventilation. Hypoventilation occurs either related to seizure activity or ICP elevation, both of which can reduce respiratory drive. Hypoventilation increases PCO_2, which causes arterial vasodilation, thereby increasing intravascular volume and ICP. This increase can cause a vicious positive feedback loop by further reducing ventilatory drive.

Signs and Symptoms

Patients can experience a variety of symptoms and signs caused by elevated ICP. These findings do not necessarily correlate with the degree of elevated pressure, though generally the higher the ICP, the more significant the neurologic findings.

As ICP increases, compression of the reticular activating system depresses the patient's level of consciousness. These findings tend to occur sequentially, with the patient progressing from an awake and alert status to progressively more lethargic states and may eventually lead to coma.

Patients may develop a variety of cognitive changes resulting from elevated ICP. Disorientation, short-term memory loss, decreased fund of knowledge, and loss of insight and judgment can occur to varying degrees.

As increasing ICP approaches pressure of the central retinal vein, the patient will usually lose the spontaneous venous pulsations that are seen on routine funduscopic examination. Further elevation of ICP exceeding the central retinal vein pressure causes swelling of the optic disks (papilledema). Papilledema does not usually occur rapidly in the setting of elevated ICP. Usually several days of elevated ICP must ensue before papilledema is evident. A patient with long-standing papilledema may have constriction of his/her visual fields and/or decreased visual acuity.

Brain masses causing elevated ICP can cause brain shifts from one intracranial compartment to another. Usually a brain shift, also known as a "herniation," is away from the mass causing the elevated ICP. Supratentorial masses may cause the brain to herniate inferiorly through the tentorial incisura. With a resulting central diencephalic herniation syndrome, the patient experiences simultaneous bilateral pupillary dilation from compression of the tectum, containing the Edinger–Westphal nucleus of the oculomotor nerve (CN III). A lateral cerebral mass, particularly if in the temporal lobe, forces the uncus of the temporal lobe to herniate through the incisura. This uncal herniation causes compression of CN III between the posterior cerebral artery and the superior cerebellar artery, resulting in unilateral pupillary dilation. In both herniation syndromes, the constrictive phase of the light reflex can also cease to function (unreactive pupils). Usually, though not always, decrease in the patient's level of consciousness precedes pupillary dysfunction.

Patients can also have light-near dissociation. Pressure on the tectum can compress the retinotectal fibers that are part of the afferent limb of the pupillary light reflex; the pupil does not constrict to light appropriately. However, those fibers involved in the afferent limb of pupillary accommodation to near vision, which travel to the tectum through other pathways, are not affected. Patients, therefore, can have pupils that constrict to accommodation but not to light. This is often a very subtle sign of elevated ICP.

Double vision may also be present. The abducens nerve (CN VI), which controls abduction of the eye, has the longest intracranial course of the cranial nerves and is at highest risk of dysfunction when ICP is elevated. Diplopia is usually more pronounced with increasing lateral gaze, either unilaterally or bilaterally.

As the dura and blood vessels are stretched by elevated ICP, the patient may experience headache. Headache is frequently described as "band like" or "pressure like." It tends to occur more commonly in the early morning and may wake the patient from sleep. While the patient is sleeping, the recumbent position decreases venous return to the heart, elevating ICP. In addition, hypoventilation that occurs during sleep will also elevate ICP, increasing the headache.

Not uncommonly, headache is associated with projectile vomiting. Vomiting occurs because of increased pressure on the area postrema.

In addition to the symptoms and signs described earlier, patients with elevated ICP often experience neurologic deficits from the compressive effects of the mass of the tumor on adjacent neural structures. These deficits can include the following: hemiparesis, aphasia, visual field deficits, hearing loss, ataxia (truncal or appendicular), and sensory loss. The presence of these findings is based on the size, location, and rapidity of growth of the mass. Slower growing tumors allow the brain to compensate; focal findings may not be evident until late in the patient's course.

Management

Mechanical and pharmacologic therapies are available to treat elevated ICP, with expectant reduction or elimination of its signs and symptoms. Some require very minimal intervention, while others are much more intensive or invasive.

Head elevation of 30 to 45 degrees is perhaps the easiest treatment available. It increases venous drainage from the brain, thereby reducing blood volume within its intravascular compartment. Head elevation poses minimal risk to the patient. Theoretically, cerebral perfusion could be diminished, but such a reduction is negligible in a patient with normal blood pressure.

Mannitol, an osmotic diuretic, draws fluid out of the brain and into the vascular system by increasing serum osmolarity. From the vascular spaces, the fluid follows the mannitol as the kidney excretes it. Therefore, mannitol reduces intracellular and extracellular water in the brain. Furthermore, mannitol improves blood rheology; ischemic areas of brain adjacent to the tumor mass are better perfused [4]. Mannitol is

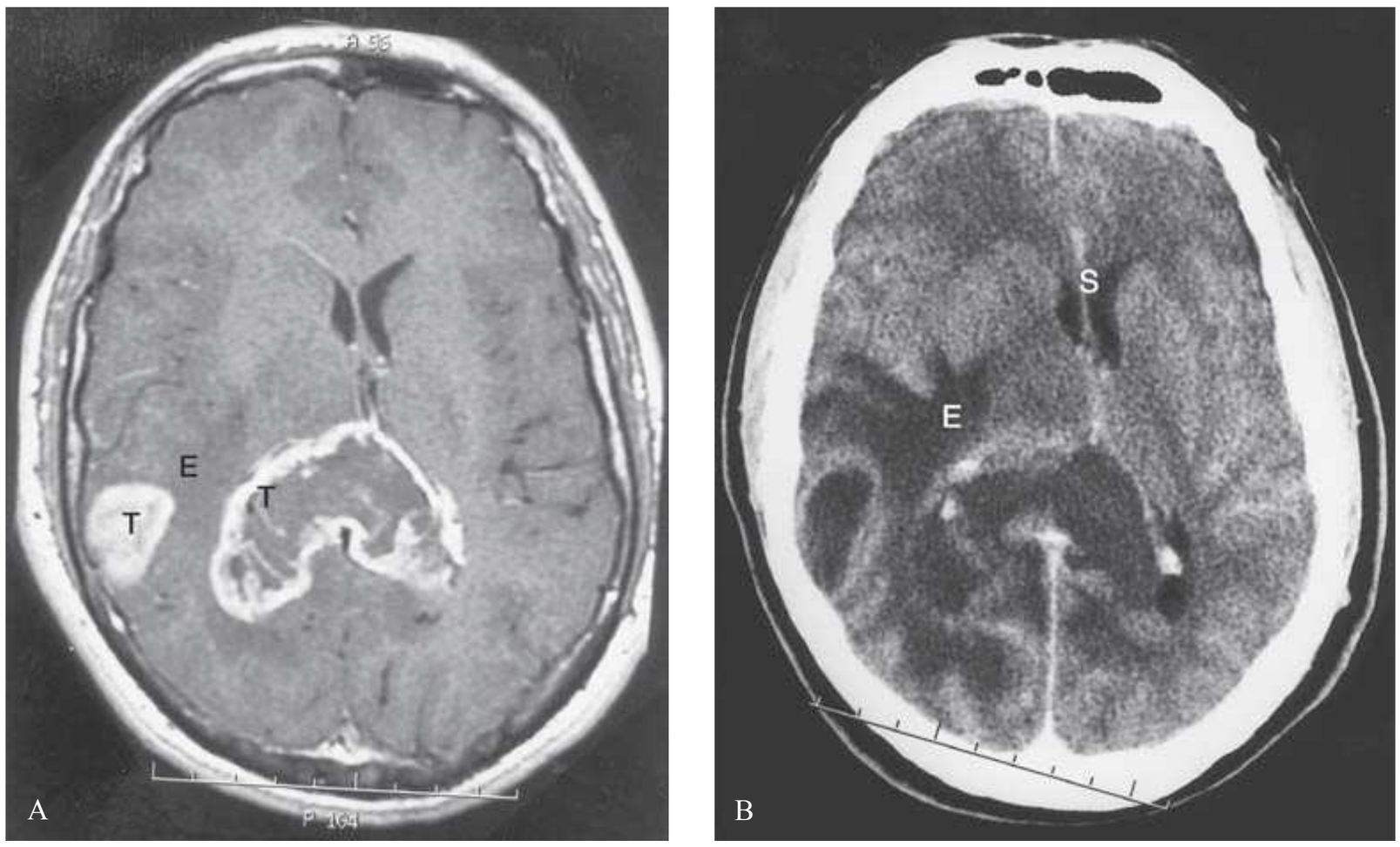

FIGURE 174.1. A: This magnetic resonance imaging, performed on a patient presenting with headache and memory lapses, shows an enhancing mass (T) involving the corpus callosum and right parietal area, with surrounding edema (E). Stereotactic biopsy revealed glioblastoma multiforme. **B:** One week following biopsy, the patient was admitted to the intensive care unit with obtundation and left hemiparesis. His computed tomography shows increased edema (E) and right-to-left midline shift (S)—parafalcine herniation. He required mannitol, increased Decadron, and surgical decompression to improve.

frequently given as an initial resuscitative dose of 1 gm per kg, followed by 0.25 gm per kg every 4 to 6 hours to maintain the diuresis and control ICP. Mannitol is quite effective in lowering ICP and/or reversing early cerebral herniation. It may also be used if patients have significant mass effect identified on neuroimaging studies to stabilize and improve their condition (Fig. 174.1). A number of potential risks are present with long-term mannitol use. Hypotension can occur in already hypovolemic patients. Patients can also become hyperosmolar and hypernatremic. Therefore, mannitol is usually withheld from the patient if serum osmolarity exceeds 320 mOsm per L. Lastly, there is some concern that mannitol may lose effectiveness if used continuously for more than 72 hours.

Furosemide (Lasix), a loop diuretic, rapidly reduces systemic circulating volume. Extracellular and intracellular water in the brain are drawn into the vascular system and are redistributed. Lasix also promotes venous pooling, leading to similar redistribution of fluids. While mannitol is generally used as the first-line agent, Lasix may be used at an initial resuscitative dose of 1 mg per kg in patients with cerebral herniation. Risks are minimal in this setting, as electrolyte abnormalities are unlikely to occur with only a single dose. In a patient who has had frequent vomiting and is already dehydrated, Lasix can cause hypotension from the additional hypovolemia.

Hypertonic saline enhances cerebral blood flow by increasing intravascular osmolarity that creates a gradient to move free water from the interstitial and intracellular compartments to the intravascular space. This is associated with an acute plasma expansion with hemodilution, increase in arterial blood pressure, and reduced vascular resistance [5]. Hypertonic saline has also been found to have some inotropic effects that appear to be derived from improvement in cardiac microcirculation and contractility [6]. However, significant polyuria has been observed in the acute setting which may lead to excessive diuresis and subsequent dehydration. Patients on hypertonic therapy should also have frequent blood draws every 6 hours to monitor serum osmolality and serum sodium. It is generally recommended to have a target serum sodium from 145 to 155 mmol per L and serum osmolality of less than 320 mOsm per L. Serum sodium should not increase more than 15 mmol per L daily and should not be allowed to drop more than 10 mmol per L daily to decrease the risk of central pontine myelinolysis [7].

Glucocorticosteroids can markedly improve symptoms of elevated ICP and/or mass effect in patients with cerebral neoplasms. They work by stabilizing cell membranes and reducing vasogenic edema [8,9]. Dexamethasone (Decadron) is the most commonly used glucocorticosteroid. An initial dose of 10 to 20 mg is followed by 4 to 6 mg every 4 to 6 hours, depending on the severity of the patient's clinical condition. Solu-Medrol (100 mg initially, and then 20 to 40 mg every 4 to 6 hours) is another option. Glucocorticosteroids are the medical mainstay of brain tumor care because their effects are sustained over time. A patient with vasogenic edema from tumor may require steroids for a significant period of time. In the short term, steroids can cause hyperglycemia and exacerbate diabetes mellitus, changing the patient's insulin requirements. Gastrointestinal hemorrhage or ulceration can occur; H_2 blockers, such as Pepcid, Nexium, or Zantac, are frequently given prophylactically. The stimulatory effect of steroids frequently disrupts sleep. Long-term use of steroids may be associated with proximal muscle weakness, avascular necrosis of the femoral head, easy bruising, and other findings of Cushing's syndrome.

In contrast to cerebral vasodilation caused by hypoventilation, hypocarbia from hyperventilation causes cerebral vasoconstriction, which reduces the arterial intravascular blood volume within the brain. Hyperventilation can therefore rapidly reduce ICP and reverse a cerebral herniation syndrome. Although initial hyperventilation can be performed with an AMBU bag valve mask, sustained hyperventilation requires endotracheal intubation and mechanical ventilation of the patient. Moderation of hyperventilation is necessary because at PCO_2 less than 25 mm Hg, cerebral ischemia may result from profound vasoconstriction. A vasodilatory rebound from hyperventilation occurs after approximately 24 hours, thereby negating its positive effects if hyperventilation is used chronically [10].

One of the most effective means of rapidly reducing ICP is to drain CSF. Such a maneuver is effective whether or not the patient has hydrocephalus. In a patient with a brain tumor, the safest method of draining CSF is to place a ventriculostomy, a catheter usually passed into the frontal horn of the lateral ventricle via a small hole drilled through the skull. The procedure can be performed by a neurosurgeon at the bedside. After placement of a ventriculostomy, drainage of CSF into a bag at bedside can reduce ICP. The catheter can also be coupled to a pressure transducer so that ICP can be measured. Usually, CSF is drained if ICP exceeds 15 to 20 mm Hg. The risks of the procedure include hemorrhage and infection. Therefore, coagulation studies are appropriate before the procedure is done, especially in patients who have received recent chemotherapy. The risk of infection increases the longer the catheter remains in place. Sometimes, prophylactic antibiotics are used.

Regardless of what means are necessary to stabilize and/or resuscitate the patient, the best means of controlling ICP in long term is to remove the tumor if possible. Unfortunately, some tumors are unresectable. Gliomas or metastases involving the thalamus or basal ganglia are generally not resected, except in unusual circumstances. In these instances, medical management is necessary to control ICP until adjuvant therapy, such as radiation therapy, can shrink the tumor and reduce its edema-producing capabilities. The same rationale applies to patients with multifocal cerebral masses; patients with more than one metastasis do not usually have multiple operations to resect each tumor, especially if symptoms are controllable with steroids. On the other hand, if the tumor is resectable, its removal can relieve the brain of the extra mass, relieve obstruction to the flow of CSF, and reduce vasogenic edema. In addition to relieving the signs and symptoms of elevated ICP, tumor resection can also relieve the effects of compression on the surrounding brain, improving lateralizing findings. Some tumors can be removed completely. These include meningiomas, vestibular schwannomas, craniopharyngiomas, pituitary adenomas, and metastatic tumors. Microscopic disease may still be present in the tumor bed, particularly in the case of metastases or craniopharyngioma, which may require adjuvant therapy, but ICP can be well controlled. Primary glial neoplasms, however, cannot be completely removed in most cases. The bulk of tumor can be resected, and postoperative neurodiagnostic images may show no residual tumor, but most of these tumors have infiltrating fingers of tumor still present. Even so, removing tumor bulk can alleviate elevated ICP; edema can sometimes be exacerbated with only partial resection, so caution is required.

HYDROCEPHALUS

Brain tumors often can cause hydrocephalus, a situation in which the patient has an increased volume of CSF under increased pressure. Hydrocephalus is typically associated with enlargement of the ventricular system (or a portion thereof) and compression of the normal brain parenchyma. A patient with hydrocephalus may require urgent or emergent intensive care monitoring and treatment. Hydrocephalus is a special case of elevated ICP and warrants separate discussion.

Etiology

Hydrocephalus can occur from a variety of mechanisms in patients with brain tumors. It is as important to identify the etiology of the hydrocephalus as its presence because the definitive treatment of hydrocephalus will be based on its mechanism of formation. Some tumors, as discussed later, are more likely to be associated with certain mechanisms of hydrocephalus than others.

Leptomeningeal infiltration by tumor cells in the subarachnoid space can prevent the absorption of CSF by the arachnoid granulations, either by occluding the granulations or preventing the flow of CSF from the outlet foramen of the fourth ventricle around the dorsolateral convexities to the granulations. Metastatic tumors from the lung, breast, lymphoma, and leukemia are the most frequently involved systemic tumors; primary tumors behaving in this fashion include primitive neuroectodermal tumors (i.e., medulloblastoma), ependymoblastoma, and glioblastoma multiforme. A patient with carcinomatous meningitis will frequently have a stiff neck or cranial neuropathy in addition to symptoms and signs of elevated ICP.

Large extra-axial "benign" tumors, usually in the posterior fossa, can cause hydrocephalus (Fig. 174.2). These tumors include those in the cerebellopontine angle, such as meningioma or vestibular schwannoma. These tumors displace the cerebellar hemisphere and obstruct the fourth ventricle to prevent adequate circulation of CSF. Rarely a choroid plexus papilloma can emerge from the foramen of Luschka and similarly compress the cerebellar hemisphere. Meningiomas of the clivus or tentorium can also displace CSF pathways with resulting hydrocephalus.

Some tumors may originate in a ventricle or protrude into a ventricle and occlude CSF pathways, thus producing hydrocephalus. These tumors include medulloblastoma, ependymoma, choroid plexus papilloma, intraventricular meningioma, colloid cyst, giant cell astrocytoma of tuberous sclerosis, and pineal region tumors.

Parenchymal tumors often can occlude CSF pathways. Primary or metastatic tumors in the thalamus or basal ganglia can displace brain parenchyma and occlude the foramen of Monro or the third ventricle [11]. Tumors in the pineal region may occlude the posterior third ventricle or cerebral aqueduct (Fig. 174.3). Brain stem gliomas or tumors in the cerebellar hemispheres can compress the fourth ventricle [12].

Symptoms and Signs

The clinical picture of a patient with hydrocephalus is frequently the same as that of a patient with elevated ICP. In fact, hydrocephalus must be considered in the differential diagnosis for causes of elevated ICP. Patients with midline masses or carcinomatous meningitis usually do not have lateralizing neurologic deficits such as hemiparesis. Those patients with unilateral brain masses may have lateralizing deficits from compression of the previously normally, but marginally, functioning brain by the progressive hydrocephalus.

Evaluation

If hydrocephalus is suspected, evaluation should proceed promptly. Two questions must be answered—"Does the patient have hydrocephalus?" and "What is the cause of the hydrocephalus?" Either MRI or CT can answer these questions. Because MRI delineates better anatomic definition of the brain, more readily illustrates the relationship of the lesion to CSF pathways, and shows these features in multiple planes, MRI with gadolinium is the preferred study. Sometimes, however, the patient is too ill to obtain an MRI easily, or MRI is not readily available. In these circumstances, a CT scan with IV contrast is sufficient. The purpose of the contrast agent with either study is to characterize the location of the lesion and its relationship to CSF pathways better. The addition of proton magnetic resonance spectroscopy to standard anatomic MRI

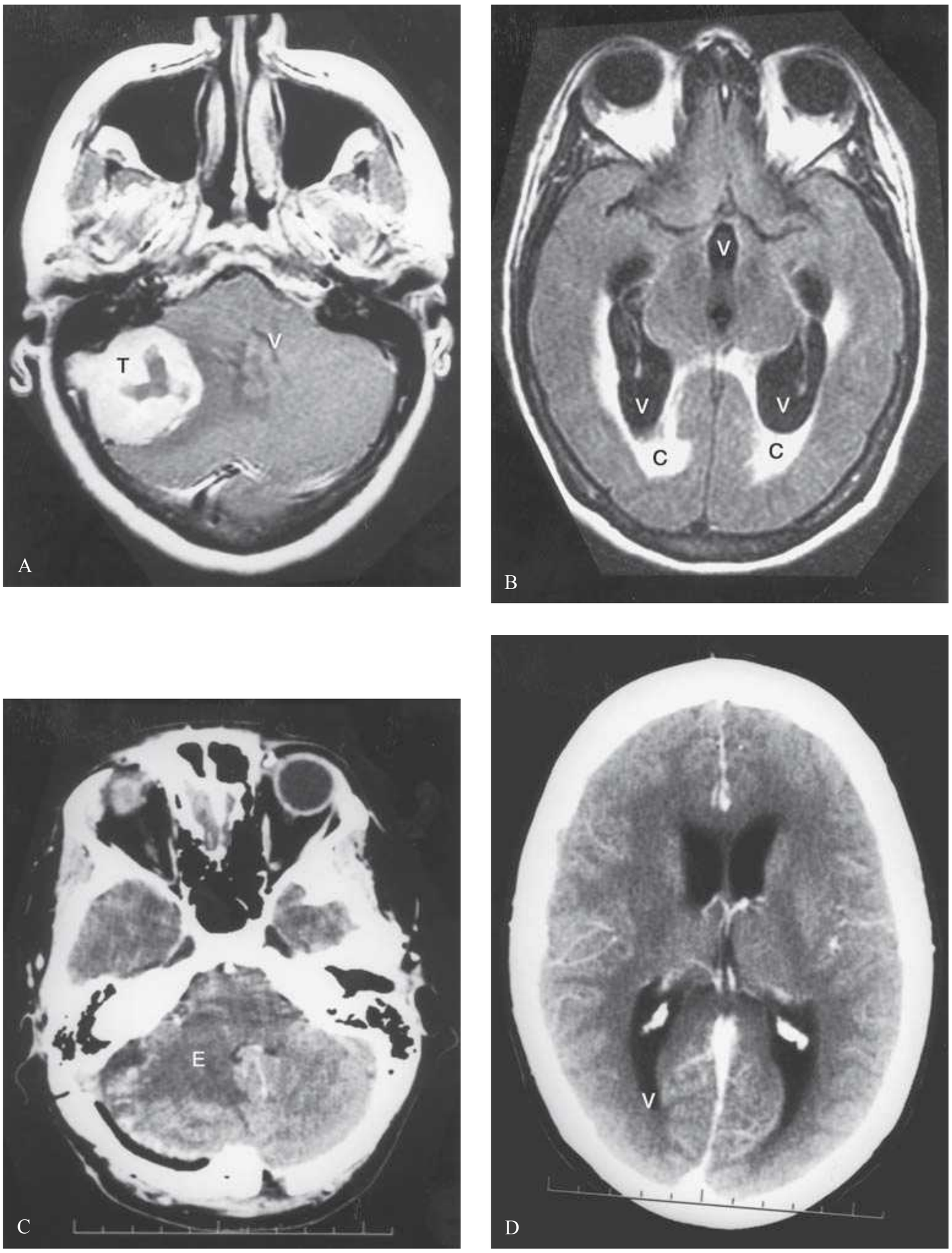

FIGURE 174.2. A: This magnetic resonance imaging (MRI), performed on a patient presenting with headache and obtundation, shows an enhancing mass in the right cerebellopontine angle (T) with displacement of the fourth ventricle (V) to the left. **B:** Additional views of the MRI show hydrocephalus, with enlarged, rounded ventricles (V) and transependymal spread of cerebrospinal fluid (CSF) (C). A ventriculostomy to drain CSF was placed to temporize the patient prior to surgery. **C:** After resection of the tumor, a meningioma, the fourth ventricle, returns toward its normal position. Edema (E) in the cerebellar hemisphere is still present. **D:** Hydrocephalus has resolved, with the ventricle (V) returning to normal size and shape.

may improve the diagnostic accuracy in assessing intracranial mass lesions.

Management

The appropriate intervention for a patient with hydrocephalus depends on several factors. These include the cause of the hydrocephalus, the anatomic location of the obstruction to CSF flow, and the patient's clinical condition.

In patients experiencing rapidly progressive deterioration, such as cerebral herniation, emergent management with a ventriculostomy, as described previously, to divert CSF temporarily can improve the patient's clinical picture. Usually, the drainage chamber is set so that the system can be opened intermittently to drain CSF for ICP greater than 20 mm Hg. Some patients, however, require a lower ICP to achieve neurologic improvement, so the system can be opened for lower pressures. An alternative method of draining CSF in patients with hydrocephalus is to set the system to drain CSF continuously at a particular

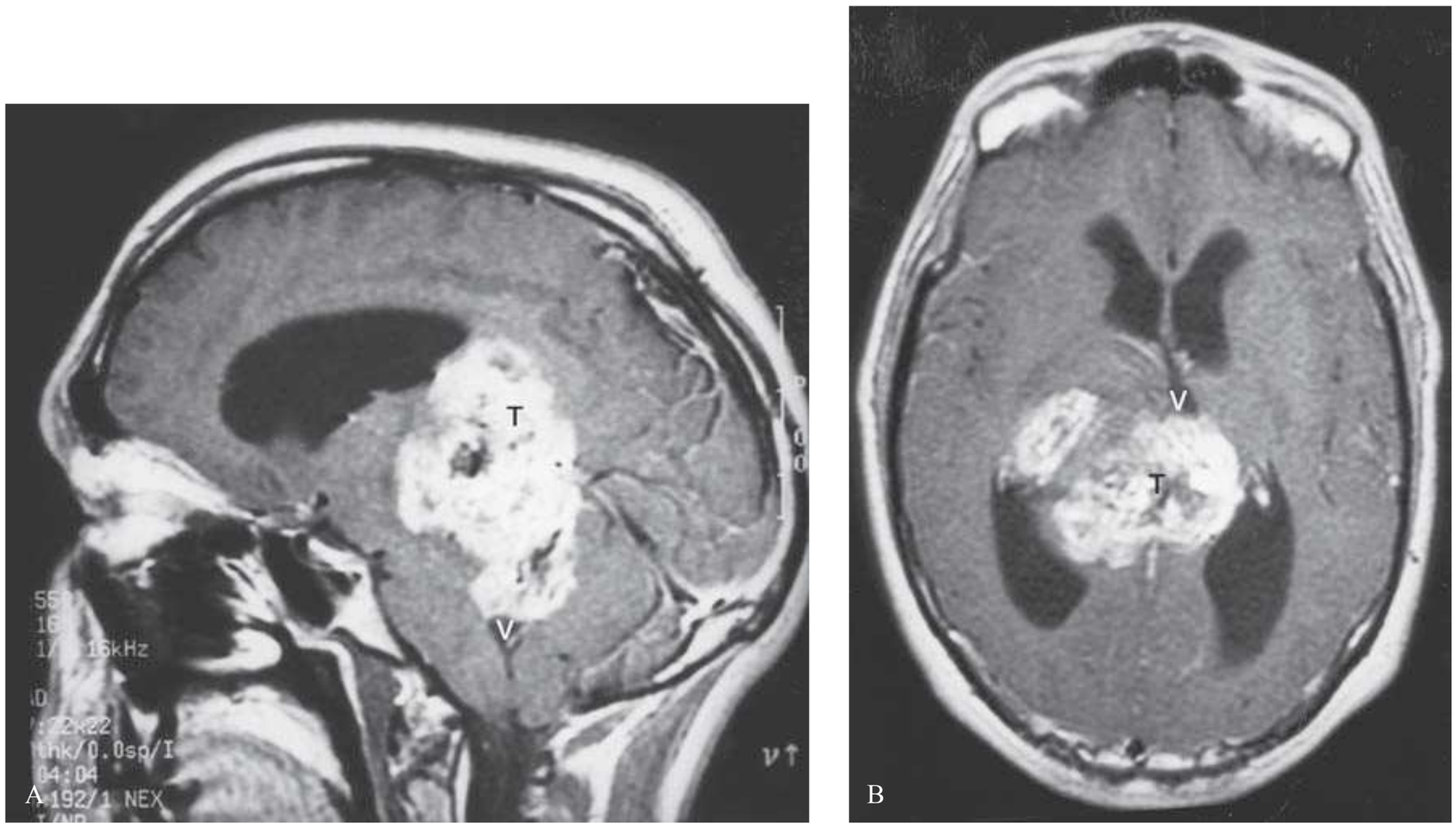

FIGURE 174.3. A: This sagittal magnetic resonance imaging on a patient with headache, lethargy, and diffuse weakness shows an enhancing mass (T) extending from the pineal region to the fourth ventricle (V). **B:** Axial views show the tumor (T) compressing the third ventricle (V) with hydrocephalus. Despite an aggressive surgical resection of this glioblastoma multiforme, the patient subsequently developed recurrent hydrocephalus and required a ventriculoperitoneal shunt.

pressure, for instance, at 15 mm Hg. ICP is then recorded on an hourly basis. This technique of CSF drainage should be approached with some caution as large volumes of CSF may drain if the patient strains or coughs, increasing intrathoracic pressure and therefore ICP temporarily. If too much CSF drains, patients may develop subdural or intraparenchymal hemorrhages.

A patient may have only mild hydrocephalus and not be significantly impaired clinically. Emergent intervention may not be necessary, and the patient can be stabilized with Decadron with or without mannitol or other hyperosmolar agent. In this situation, resection of the tumor can provide long-term treatment of hydrocephalus by decompressing the CSF pathways, particularly with posterior fossa or pineal region tumors. The patient may not require CSF diversion at all. Surgery should proceed in a timely fashion, though.

Occasionally, hydrocephalus does not respond to surgical decompression alone. Anatomic considerations are frequently responsible. It may not be possible to resect enough tumor to decompress the CSF pathways. Alternatively, absorptive capabilities may be compromised by inflammatory process from blood or tumor products. In these cases, a permanent shunt, usually from a lateral ventricle to the peritoneum (ventriculoperitoneal), is necessary to treat the hydrocephalus. This procedure is performed in the operating room. Shunts are usually well tolerated and very effective. One concern in a patient with a tumor in which malignant cells are present in the CSF is that the patient will have intraperitoneal spread of tumor via the shunt. This complication occurs uncommonly, though. Persistent symptomatic hydrocephalus dictates that the shunt be placed regardless of this concern.

A more commonly occurring concern in a patient with hydrocephalus who has been shunted is shunt malfunction [13]. Cellular debris, proteinaceous material, or normal choroid plexus can occasionally occlude a shunt. This occurrence is manifested by symptoms and signs of hydrocephalus and elevated ICP. Treatment requires operative revision of the occluded portion of the shunt, usually with replacement of the ventricular catheter or the valve.

Hydrocephalus can be somewhat problematic to treat in a patient with a tumor adjacent to the third ventricle. In this uncommon situation, the lateral ventricles may not communicate with each other through the third ventricle. In the most extreme case, the frontal horns of the lateral ventricles do not communicate with the occipital and temporal horns. Therefore, a single shunt will be ineffective in relieving the CSF obstruction. A ventriculogram, in which intrathecal contrast is placed into the lateral ventricle via a ventricular catheter (either a ventriculostomy or the ventricular portion of a shunt), can define the nature of the obstruction. The patient may require two, three, or even four ventricular catheters to drain CSF adequately. Tumors where this problem should be of concern include craniopharyngioma, central neurocytoma, pilocytic astrocytoma of the hypothalamus, and glioblastoma, among other tumors involving the medial septal structures of the brain.

SEIZURE

Seizures are a common occurrence in patients with brain tumors. About 40% of patients with gliomas initially present to medical attention with seizure; about 55% of glioma patients have a seizure at some point in the course of their disease. Some low-grade gliomas, such as oligodendroglioma, have a very high likelihood of seizure. Approximately 20% of patients with metastatic tumors have a seizure at some time [14,15].

Seizures may be focal or generalized. A patient remains conscious during a focal seizure. The seizure may be a motor seizure in which the patient's mouth twitches or an extremity moves uncontrollably for a period of time. With a dominant hemisphere lesion, aphasia may also occur. During a generalized seizure, the patient loses consciousness. Tonic–clonic movements may occur, and the patient may lose bladder control or bite their tongue. A patient can also experience status

epilepticus, a series of seizures occurring in rapid succession with the patient not regaining consciousness between seizures. Status epilepticus is a medical emergency that is addressed in Chapter 172. Occasionally, a patient can have a seizure that is not witnessed or is subclinical in activity. The patient experiences a neurologic deficit, which subsequently improves, leaving healthcare providers puzzled as to the etiology of the transient deficit.

Further evaluation of the known brain tumor patient with seizure is necessary. A seizure can occur in a patient with a known brain tumor for a number of reasons. The most common reason is that the patient's anticonvulsant medication level(s) is (are) subtherapeutic. Drug requirements may change as steroid requirements change; Decadron may interact with Dilantin to lower serum levels [16,17]. Serum drug levels are therefore essential. Other reasons for seizure include a change in the character of the tumor. The tumor may have grown in size [18] or a hemorrhage within the tumor may have occurred. A CT scan of the head without contrast helps to differentiate among these possibilities.

Treatment

While a single generalized seizure usually does not have long-term consequences, such an event may precipitate rapid deterioration in a patient with elevated ICP. The associated hypercarbia from hypoventilation can increase ICP substantially; a stable patient can rapidly deteriorate even to the point of developing a herniation syndrome. Hypoxia can further compromise brain function by causing damage similar to cerebral ischemia, especially in the area already affected by the tumor. Prompt intervention is therefore necessary.

Maintenance of an adequate airway and reestablishment of adequate ventilation is essential. Oxygen should be provided to the patient. Intubation and mechanical ventilation may be required if the patient experiences hypoventilation.

The best medication to stop seizure activity in patients with status epilepticus is Ativan. The initial dose is 2 mg IV, and the dose is repeated acutely every 5 minutes as needed, up to a total of 8 mg until the seizure activity stops. Should 8 mg be required, mechanical ventilation will likely be required. Dilantin (15 mg per kg IV) or phenobarbital (15 mg per kg IV) must be used acutely in conjunction with Ativan, as the Ativan is only for short-term seizure control.

Prophylactic anticonvulsants administered without a seizure having occurred are rarely indicated unless the patient is going to surgery [19]. Following a seizure, the patient should be started on an anticonvulsant, such as Dilantin. The initial loading dose is 15 mg per kg intravenously, with oral or intravenous maintenance dosing of 100 mg three times daily or 200 mg twice a day. Phenobarbital, although more sedating than Dilantin, can also be used. Both Dilantin (or fosphenytoin) and phenobarbital are available in intravenous forms and may be used if the patient is unable to take oral or enteral medications. Tegretol, on the other hand, is only available in an oral form, so it cannot be used in status epilepticus or in patients who cannot tolerate enteral intake. Keppra is available in both oral and intravenous formulas, has fewer interactions with other medications, and tends to have less sedating side effects.

POSTOPERATIVE COMPLICATIONS

One of the most common reasons for a patient with a neuro-oncological illness to be admitted to an ICU is for observation following a neurosurgical procedure. This period of observation may just be overnight or it may be longer, being dictated by the patient's neurologic and/or medical condition. Although perioperative mortality is less than 2%, medical or neurologic complications may occur in up to 30% of cases; older patients and those with increased neurologic deficits are more likely to suffer these morbidities [20]. Therefore, a variety of intraoperative and postoperative complications must be recognized before the patient's neurologic or medical status is irreversibly compromised. Intervention can then proceed promptly.

To anticipate potential complications, vital signs and neuro-checks are taken hourly by nurses in the ICU. One of the most important components of the neuro-checks is the patient's level of consciousness, usually denoted by the Glasgow Coma Scale (GCS) score [21,22]. This three-part score consists of patient responses in eye opening, motor, and verbal spheres. Originally developed to document the level of consciousness in patients with head trauma, use of the GCS can readily, reliably, and reproducibly identify changes in the patient's level of consciousness—either deterioration or improvement. Furthermore, its use can help evaluate the effectiveness of interventions by the reported trends. Other components of neuro-checks include pupillary light responses, orientation, and motor function. Any decrement in function warrants prompt evaluation. Such an evaluation should include a CT or MRI scan of the head, serum electrolytes, blood gases, and anticonvulsant level(s). Other tests may be required based on the patient's condition. Recent technological advancements have allowed for production of mobile CT scanners for use in the ICU. While the resolution is significantly less than traditional CT scanning, the mobile CT scanner can be utilized to ascertain gross intracranial pathology in patients who may otherwise be too unstable for transport. Evaluation of the ICU patient for intracerebral hemorrhage or increased ventricular size can be performed at the patient's bedside and allow for rapid diagnosis in patients with acute changes in mental status. Mobile CT scanning has also been utilized intraoperatively during resection of glial tumors, which may allow for more complete resection of intracranial pathology [23].

Intracranial Hemorrhage

One of the most dramatic complications that can occur in the postoperative period is intracranial hemorrhage. Significant hemorrhage usually becomes evident within 6 to 12 hours after the completion of surgery. A patient can bleed into the tumor bed (Fig. 174.4), or into the subdural or epidural spaces. Although steps are taken at surgery to prevent such complications, oozing from small vessels in the tumor bed can occur. Traction by the brain, slackened by tumor removal, mannitol, Lasix, hypertonic saline, hyperventilation, and CSF drainage, can tear or stretch draining veins, leading to blood accumulation in the subdural space. Because the dura is separated from the bone to perform the craniotomy, the epidural space is no longer just a potential space; rather, it is a real space into which blood can ooze from underneath the bone edges and accumulate. Patients who experience significant hypertension or persistent coughing and "bucking" as they emerge from anesthesia are at greater risk for developing postoperative hemorrhage. Hypertension can cause bleeding from arterial-side vessels. The increase in intrathoracic pressure that occurs with coughing or bucking against the endotracheal tube can precipitate venous-side bleeding, as can thrombosis in a draining vein from manipulation.

Postoperative hemorrhage should be suspected in a patient who fails to emerge adequately from anesthesia. Intracranial hemorrhage should also be a concern if the patient deteriorates following emergence from anesthesia and develops progressive decline in level of consciousness, pupillary abnormalities, or

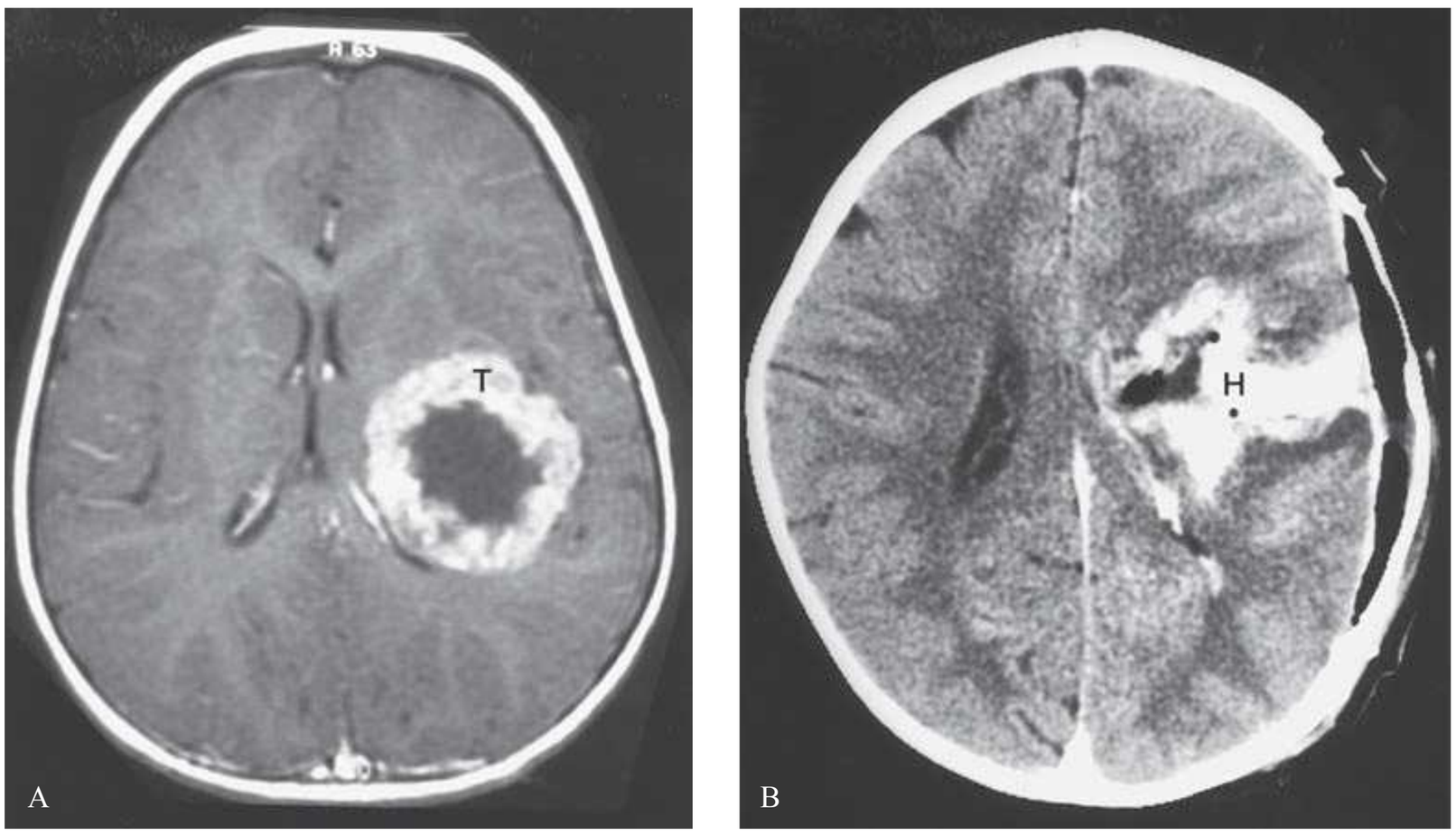

FIGURE 174.4. A: This magnetic resonance imaging on a 2-year-old boy shows a large enhancing mass (T) in the left temporoparietal area. **B:** Immediately following surgery to remove the rhabdoid neuroepithelial tumor, the patient had sustained hypertension and awakened slowly from her anesthesia with a mild right hemiparesis. This computed tomography scan shows hemorrhage (H) in the tumor bed. With blood pressure control and observation, the patient recovered to a normal level of consciousness with resolution of her hemiparesis over several days.

new motor deficits. Emergent evaluation with a CT scan is indicated. Coagulation deficits, particularly in patients who have had chemotherapy recently or who have liver disease, should be ruled out with laboratory testing for prothrombin time, partial thromboplastin time, and platelet count.

Should a significant intracranial hemorrhage be identified, the patient may need to return to the operating room to evacuate the hemorrhage. Mannitol and reintubation may be required to stabilize the patient's condition. Occasionally, if the neurologic deterioration is mild, observation or mannitol by itself may be sufficient intervention. As the blood degrades over time and edema subsides, the patient should improve clinically. Frequent follow-up CT scanning is necessary in nonoperative management to evaluate the status of the hemorrhage and surrounding brain.

Cerebral Edema

Manipulation of the tumor and adjacent brain can lead to cerebral edema. Clinical signs can appear quite similar to postoperative hemorrhage, although deficits from edema tend to occur in a more delayed fashion. Prompt treatment with mannitol and Decadron is indicated following a CT scan to confirm the etiology of the patient's neurologic change.

Endocrinopathy

Pituitary tumors may be associated with hypersecretory or hyposecretory states. Other tumors in the sella and parasellar areas may also be associated with endocrinopathy, usually hypopituitarism. Surgery for tumors in these locations can cause endocrine deficits too. Most endocrinopathies encountered in the ICU are related to pituitary hypofunction.

The major neurologically related endocrinopathy evident in the ICU setting is diabetes insipidus, most commonly after craniopharyngioma or pituitary tumor resection. It usually occurs between 18 and 36 hours following surgery. Signs of diabetes insipidus include an increase in urine output greater than 200 mL per hour for 2 consecutive hours, a corresponding drop in urine specific gravity to less than 1.005, and an increase in serum sodium to greater than 147 mEq per L. A patient who is conscious usually experiences increased thirst. Hypotension can occur if the complication is not recognized early. Treatment with DDAVP 0.25 mL (1 mg) subcutaneously or intravenously is indicated when diabetes insipidus is recognized. DDAVP is usually given twice a day. One must be cautious that the patient is actually experiencing diabetes insipidus and is not just mobilizing surgical fluids. In a patient who has had a transsphenoidal resection of a pituitary tumor, increased thirst may be present only because the patient's nasal packs force him/her to mouth-breathe. Diabetes insipidus is usually transient, resolving by about 72 hours postoperatively, so the patient should be permitted to drink freely. For this reason, over the first several days, it is probably better to give the DDAVP only when the patient's findings indicate treatment is appropriate. Occasionally, diabetes insipidus may be permanent. Intranasal DDAVP 0.2 mL at night is an effective dosing regime for these patients in the subacute to chronic phases of diabetes insipidus.

Low serum cortisol is frequently not observed acutely in the ICU as patients are usually on glucocorticosteroids. However, after abrupt cessation of steroid treatment, a patient may experience an Addisonian crisis. Hypotension, weakness, and fatigue are the major findings. Because the steroid depletion is acute, hyponatremia, hyperkalemia, and hyperpigmentation generally are not observed. Treatment should be instituted promptly with hydrocortisone 100 mg IV every 6 hours.

Hypothyroidism usually does not become evident for at least a week following surgical injury to the pituitary gland or hypothalamus. Fatigue, lethargy, and hyporeflexia may be present. Laboratory testing shows low T4 and free thyroxine uptake, as well as low thyroid-stimulating hormone. For a patient with a sellar or parasellar tumor, preoperative recognition and treatment of hypothyroidism help prevent this endocrinopathy from becoming evident postoperatively.

Postoperative Central Nervous System Infections

Infections of the central nervous system are uncommon in neuro-oncology patients. Perioperative antibiotics, such as cefazolin 1 gm IV just prior to the skin incision and then for several doses following surgery, reduce the infection rate [24,25]. The likelihood of a postoperative infection in the absence of CSF leak in a clean operative field (one which does not involve the paranasal or mastoid sinuses) is about 0.8% [26]. Should CSF leak occur or if operative time is extended, the risk of infection increases. Infection can occur in any of the operative spaces.

A patient may develop wound cellulitis. This superficial infection is associated with erythema, induration, and sometimes wound drainage or breakdown. The patient may have a fever and/or elevated white blood cell count. This complication usually occurs within the first week after surgery. It will usually respond to antistaphylococcal antibiotics within several days. A 10-day course of antibiotics is usually sufficient. If drainage from the wound is present, then it should be cultured to tailor antibiotics appropriately.

Bone flap infections are more involved than simple postoperative cellulitis. They tend to occur in a delayed fashion. Drainage from a breakdown in the suture line or from the scalp near the bone flap will usually be present and should be cultured. White blood cell count and erythrocyte sedimentation rate are usually elevated. A CT scan of the head may show an epidural purulent collection or a moth-eaten appearance of the bone. Parenteral antibiotics for several weeks are necessary, though usually insufficient by themselves. Unfortunately, because the bone flap is devascularized, removal of the infected bone flap is usually necessary to eradicate the infection. A cranioplasty can be performed 6 months after the infection has resolved to reconstitute the integrity of the skull.

Postoperative meningitis occurs infrequently, usually in the first week after surgery. Fever without another focus of infection, or "stiff neck" are usually present. Lumbar puncture is essential to rule out meningitis. Usually a CT scan is performed first to rule out a structural cause of the change in level of consciousness that frequently accompanies the infection. The occurrence of meningitis often necessitates the return of the patient from the floor to the ICU. If meningitis is suspected, parenteral antibiotics should be instituted immediately after lumbar puncture. If cultures are positive, or the glucose is low in the presence of a neutrophil pleocytosis in the CSF, then a 14-day course of broad-spectrum antibiotics is appropriate [27]. If the cultures are negative, the antibiotics can be stopped.

A patient with cerebral empyema or abscess after surgery for a brain tumor typically experiences headache and other symptoms and signs of elevated ICP. Lateralizing neurologic deficits are often present. A CT or MRI scan with IV contrast is essential. In subdural or epidural empyema, the dura or arachnoid usually densely enhances with an adjacent low-density fluid collection. An abscess will show ring enhancement at the surgical site, which can look very similar to the original tumor in some cases. Suspicion of empyema or abscess necessitates an urgent return to the operating room to drain the collection of pus and obtain cultures. Six weeks of parenteral antibiotics are then necessary.

Radiation-Related Complications

Most patients with high-grade primary brain tumors or metastatic tumors will receive external beam radiation as an adjuvant therapy to control tumor growth for as long as possible. Although such treatment is usually tolerated without difficulty, a patient may have worsening of his/her neurologic condition during treatment. This "early effect" worsening is usually related to cerebral edema. CT scan and MRI show an increase in low density/intensity signal around the tumor volume. The edema tends to be responsive to high-dose glucocorticosteroids. Once the patient improves, steroids can be slowly tapered to usual maintenance doses.

Much more rarely, a patient may deteriorate in a delayed fashion. "Late effects" occur about 6 to 24 months after completing radiation therapy [28]. Imaging studies show intense enhancement in the area treated. It is often difficult to differentiate radiation necrosis from tumor recurrence solely on the basis of a contrast CT or gadolinium MRI as the two entities, particularly in the case of primary glioma, look similar. Single positron emitting CT, MR spectroscopy, or MR arterial spin labeling studies can often be helpful in establishing the diagnosis; tumor tends to have high metabolic activity and blood flow, while radiation necrosis is metabolically hypoactive. Sometimes, a stereotactic brain biopsy may be required to make a definitive diagnosis. High glucocorticosteroid doses are necessary to treat radiation necrosis. Mannitol may initially be required if the patient has significantly deteriorated in order to stabilize the patient and allow steroids the time to work. Occasionally, a craniotomy to remove the necrotic tissue is required as well.

Single-fraction stereotactic radiosurgery is more likely to be associated with the development of symptomatic radiation necrosis than conventional external beam radiation. In radiosurgery, the patient receives a high dose of radiation to the tumor volume, sparing the surrounding normal brain. Even so, the radiation that the surrounding brain receives may exceed its tolerance if previous radiation therapy was also used. Treatment is as described earlier. Approximately 13% to 50% of gliomas and 10% of metastatic tumors treated with radiosurgery may require subsequent surgical decompression [29,30].

SPINAL TUMORS

Spinal tumors are much less common than intracranial tumors. Most patients with spine tumors do not require ICU treatment. Exceptions include patients with spinal tumors involving the cervical spine or those who have had transthoracic approaches to thoracic spinal neoplasms. These patients will frequently have ICU treatment requirements.

A patient with a cervical spinal cord tumor may have compromise of intracostal musculature or decreased diaphragmatic function with resultant inability to maintain adequate ventilation, depending on the level of the tumor. Vital capacity should be assessed every 6 hours, as its decrement will usually be noted before respiratory insufficiency occurs. A decrease below 10 to 12 cc per kg usually requires semiurgent intubation and mechanical ventilation. Once oxygen desaturation is noted, the patient decompensates rapidly, and emergency resuscitative efforts may be required.

After spinal cord surgery, a patient may experience a temporary ileus. Bowel sounds may stop and the abdomen may become distended. Frequently the patient will need a nasogastric tube. No oral or enteral intake is appropriate until the ileus subsides. Medications will need to be given parenterally.

A spinal cord tumor is not infrequently associated with development of a neurogenic bladder. The patient often requires a Foley catheter to decompress the bladder; although such intervention is necessary, it can mask the findings. Attention to urinary retention following removal of the Foley is in order. Urinary tract infections are also not uncommon, either related to long-term Foley placement or suboptimal bladder emptying.

A long-term intermittent catheterization program to maintain bladder volumes less than 500 cc is necessary if urinary retention persists.

SYSTEMIC COMPLICATIONS

Not infrequently, patients with neuro-oncological primary problems will experience systemic complications necessitating evaluation and treatment in the ICU.

Deep Venous Thrombosis and Pulmonary Embolism

Patients with brain and spinal cord tumors are at risk for development of deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE). Decreased movement of an extremity from a motor deficit predisposes the patient to develop a DVT. Additionally, tumors may be associated with a hypercoagulable state, which can also lead to the development of DVT. Precautions, including TED stockings or sequential leg compression boots, should be taken to prevent DVT from developing. Subcutaneous heparin (5,000 units twice a day) or prophylactic enoxaparin is also an option. Venous duplex scanning can recognize DVT before it becomes symptomatic.

DVT should be suspected if the patient complains of leg pain or has a fever or elevated white count without a clear explanation. PE usually presents with shortness of breath and chest pain. Blood gases show hypocarbia with mild to moderate hypoxia. Administration of oxygen is necessary and prompt evaluation with chest x-ray, V/Q scan, and/or spiral CT of the chest is in order.

Once identified, treatment with anticoagulation may be problematic, especially in the immediate postoperative period [31,32]. In a patient at high risk for PE, some advocate anticoagulation beginning 3 to 5 days after surgery [33], though this time frame is not accepted by all. Most often the patient will have placement of an inferior vena cava (Greenfield) filter to prevent PE until 2 weeks have transpired from surgery. After that time, the use of anticoagulation is much less risky and is the preferred treatment.

Cerebral Infarction

Approximately 15% of cancer patients have significant cerebrovascular pathology noted at autopsy [34]. Patients with primary brain neoplasms are also at risk for cerebral infarction. This complication may be related to the hypercoagulable state present in patients with malignancies. Alternatively, because these patients may be older with premorbid atherosclerosis, they may suffer cerebral infarction. This event should be differentiated from hemorrhage into a tumor or progressive tumor enlargement. CT scan or MRI scanning is essential. The issues regarding anticoagulation must be addressed as with DVT or PE. Daily aspirin is generally safe. Coumadin, if indicated, should be reserved for patients who have not had hemorrhage into the tumor and who are at least 2 weeks postoperative.

Systemic Infections

Systemic infections are not uncommon, and most often include pneumonia, urinary tract infections, or sepsis secondary to line placement. Their management does not differ in the neuro-oncology patient from any other patient in the ICU.

END OF LIFE IN THE ICU

Unfortunately, despite the variety of available therapies, almost all primary high-grade gliomas will progress, and the patient harboring the tumor will succumb to the disease. A patient with metastatic brain disease may fail tumor treatments as well. Ideally, the patient's physicians will have discussed these possibilities as the patient begins to show signs of decline. The patient and family may decide to limit the intensity of care, and treatment in the ICU is not an issue. However, a patient may deteriorate quickly from the illness and elevated ICP before limits on treatment can be discussed and defined. When these circumstances occur, the physicians in the ICU may need to discuss limiting care with the patient and family. The most intensive interventions—surgery, ventriculostomy, and intubation for hyperventilation—may be most readily decided against. Other interventions, such as mannitol, may be withheld. Sometimes, a decision is made to stop all treatment. Abrupt cessation of Decadron generally leads to a rapid demise of the patient.

On occasion, an aggressively treated patient will continue to deteriorate. Elevated ICP can cause cardiac arrhythmias in the end stage. Prior to the onset of such cardiac difficulties, however, the patient may progress to the point of "brain death." In the United States, the definition of brain death requires that the patient is not hypotensive, hypothermic, or on paralytic or sedative medications. The etiology of the patient's condition should be known. The clinical examination shows the patient to be comatose, without any brainstem reflexes, motor responses, or spontaneous respirations, and on no sedative medications. An apnea test is also necessary. In this test, the patient is provided flow-by oxygen at 100% to maintain adequate oxygenation. The patient is disconnected from the ventilator and observed for the absence of respirations for 10 minutes (until a PCO_2 of 60 mm Hg is reached). Confirmatory tests, such as electrocerebral silence on an electroencephalogram or absence of brain blood flow on a radionucleotide cerebral flow study, can also be helpful [35]. If these criteria are present, the patient should be declared brain dead and removed from life support. Organ donation can be considered and discussed with the family, although systemic malignancy, infection, or specific organ failure would be contraindications to donation.

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CHAPTER 175 ■ GUILLAIN–BARRÉ SYNDROME

ISABELITA R. BELLA AND DAVID A. CHAD

Guillain–Barré syndrome (GBS) was described by Guillain, Barré, and Strohl in 1916 as an acute flaccid paralysis with areflexia and elevated spinal fluid protein without pleocytosis [1]. It is the most common cause of rapidly progressive weakness due to peripheral nerve involvement, with an annual incidence of 0.6 to 2.0 cases per 100,000 population [2]. For decades, GBS has been viewed as an acute inflammatory *demyelinating* polyradiculoneuropathy (AIDP) affecting nerve roots and cranial and peripheral nerves of unknown cause that occurs at all ages. In the past 20 years, the recognition of primary *axonal* forms of GBS has broadened the spectrum of GBS to include both the demyelinating form (AIDP) and axonal forms—acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN), as well as the Miller–Fisher syndrome. AIDP is the most common subtype in developed countries, while axonal forms are more common in northern China.

Over the years, it has become clear that the condition may be fatal because of respiratory failure and autonomic nervous system abnormalities [3]. It is, therefore, recognized as a potential medical and neurologic emergency that may require the use of intensive care units (ICUs) experienced in handling the complications of the illness [4].

DIAGNOSIS

Clinical Features in Acute Inflammatory Demyelinating Polyradiculoneuropathy

GBS often occurs 2 to 4 weeks after a flulike or diarrheal illness caused by a variety of infectious agents [3], including cytomegalovirus, Epstein–Barr and herpes simplex viruses, mycoplasma, chlamydia, and *Campylobacter jejuni* [5]. It can also be an early manifestation of human immunodeficiency virus (HIV) infection before the development of an immunosuppressed state [6]. Lyme disease may rarely produce a syndrome of polyradiculopathy reminiscent of GBS [7]. Other antecedent events include immunization, general surgery and renal transplantation, Hodgkin's disease, and systemic lupus erythematosus [2,3].

The illness is heralded by the presence of dysesthesias of the feet or hands, or both. The major feature is weakness that evolves rapidly (usually over days) and classically has been described as ascending from legs to arms and, in severe cases, to respiratory and bulbar muscles. Weakness may, however, start

in the cranial nerves or arms and descend to the legs or start simultaneously in the arms and legs [2]. Approximately 50% of patients reach the nadir of their clinical course by 2 weeks into the illness, 80% by 3 weeks, and 90% by 1 month [8]. Progression of symptoms beyond 4 weeks but arresting within 8 weeks has been termed *subacute inflammatory demyelinating polyneuropathy* (SIDP) [9], while progression beyond 2 months is designated *chronic inflammatory demyelinating polyradiculoneuropathy* (CIDP), a disorder with a natural history different from GBS [10]. A small percentage of patients (2% to 5%) have recurrent GBS [11].

The extent and distribution of weakness in GBS are variable. Within a few days, a patient may become quadriparetic and respirator dependent, or the illness may take a benign course and after progression for 3 weeks produce only mild weakness of the face and limbs.

Physical Findings

In a typical case of moderate severity, the physical examination discloses symmetric weakness in proximal and distal muscle groups associated with attenuation or loss of deep tendon reflexes (Table 175.1). In the early stage of illness, there is no muscle wasting or fasciculation. If the attack is particularly severe and axons are interrupted, then after a number of months, muscles undergo atrophy and scattered fasciculations may be seen (see later). Sensory loss is usually mild, although a variant of GBS is described in which sensory loss (involving large fiber modalities) is widespread, symmetric, and profound [8]. Respiratory muscles are often involved; between 10% and 25% of patients require ventilator assistance [12] initiated within 18 days (mean of 10 days) after onset [13].

There is often mild to moderate bilateral facial weakness. Mild weakness of tongue muscles and the muscles of deglutition may also develop. Ophthalmoparesis from extraocular motor nerve involvement is unusual in the typical patient with GBS. In the Miller–Fisher variant [14], however, there is ophthalmoplegia in combination with ataxia and areflexia, with little limb weakness per se. Pupillary abnormalities have been noted in GBS [15] and in the Miller–Fisher variant [16]. Papilledema is exceedingly rare [17].

Disturbances of the autonomic nervous system are found in 50% of patients and are potentially lethal [3,4]. Autonomic dysfunction takes the form of excessive or inadequate activity of the sympathetic nervous system or the parasympathetic nervous system, or both [18]. Common findings include cardiac arrhythmias (e.g., persistent sinus tachycardia, bradycardia, ventricular tachycardia, atrial flutter, atrial fibrillation, and asystole), orthostatic hypotension, and transient and persistent hypertension. Other changes include transient bladder paralysis, increased or decreased sweating, and paralytic ileus. These changes are not completely understood but may be due to inflammation of the thinly myelinated and unmyelinated axons of the peripheral autonomic nervous system. A neuropathy predominantly affecting the peripheral autonomic nervous system has been described that may have a pathogenesis similar to that of GBS [19].

TABLE 175.1

FEATURES OF GUILLAIN–BARRÉ SYNDROME

Clinical features	Laboratory features
Rapidly progressive weakness Loss of reflexes Mild dysesthesias (in AIDP) Autonomic dysfunction Respiratory compromise	Elevated cerebrospinal fluid protein Acellular cerebrospinal fluid Electromyogram: In AIDP: slow nerve conduction velocities, conduction block, dispersed responses In axonal GBS: low motor amplitudes, normal conduction velocities, and normal sensory responses in AMAN

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; GBS, Guillain–Barré syndrome.

Clinical Features in Axonal Forms

Axonal forms, like AIDP, present with rapidly progressive weakness, areflexia, and albuminocytological dissociation but differ in the following ways. AMAN patients lack sensory abnormalities and are more commonly found in northern China during summer months among children and young adults. Patients with AMAN also appear to have a more rapid progression to nadir, but recovery times are quicker [20] or similar [21] to AIDP in some patients, while others have a more prolonged course [20].

AMSAN is generally associated with a more severe course and longer time to recovery. In the series by Feasby et al. [22], these patients had a much shorter time to peak severity (1 week), more severe symptoms with more than half requiring mechanical ventilation, inexcitable motor nerves, and most had a poor recovery.

Laboratory Features

The most characteristic laboratory features of GBS are an abnormal cerebrospinal fluid (CSF) profile showing albuminocytologic dissociation (elevated protein without pleocytosis) and abnormal nerve conduction studies.

CSF examination is most helpful in reaching the diagnosis of GBS. Although the CSF profile is usually normal during the first 48 hours after onset [8], by 1 week into the illness, the CSF protein is elevated in most patients, sometimes to levels as high as 1 g per dL. Rarely, even several weeks after onset of GBS, the CSF protein remains normal and the diagnosis must rest on the presence of otherwise typical clinical features [8]. The cell count may be slightly increased but rarely exceeds 10 cells per μL; the cells are mononuclear in nature. When GBS occurs as a manifestation of HIV infection or Lyme disease, the CSF white cell count is generally increased (25 to 50 cells per μL. The CSF glucose is expected to be normal.

Electrodiagnostic studies in AIDP typically disclose slowing (less than 80% of normal) of nerve conduction velocity, most often along proximal nerve segments, with increases in distal motor and sensory latencies [8,23]. The amplitude of the evoked motor responses may be reduced because of axon loss or distal nerve conduction block, and the responses are frequently dispersed because of differential slowing along still-conducting axons [8,23]. Because the pathologic process may be restricted to spinal nerve roots and proximal nerve segments, routine nerve conduction studies may be normal on initial testing. In such cases, however, H-reflexes may be absent and F-responses may be abnormal because of involvement of the most proximal segments of the motor fibers. This, together with a normal sural nerve and abnormal upper extremity sensory action potential, is characteristic of early GBS [24].

Also early in the course of GBS, needle electrode examination electromyography may demonstrate only decreased numbers of motor unit potentials firing on voluntary effort because of nerve conduction block. Several weeks later, active denervation changes, such as fibrillation potentials and positive sharp waves, may be seen if axon loss has occurred.

In patients with the severe axonal form of GBS, AMSAN, motor and sensory nerves may be electrically inexcitable [22]. In AMAN, motor responses are low or absent while conduction velocities and sensory responses are normal [25].

Except for a mild increase in the erythrocyte sedimentation rate, hematologic studies are normal. Serum electrolytes may disclose hyponatremia [3], sometimes to a marked degree, because of inappropriate secretion of antidiuretic hormone caused by a disturbance of peripheral volume receptors. There may be evidence of previous viral or *mycoplasma* infection, such as lymphopenia or atypical lymphocytes. In some cases, evidence of recent viral infection may be sought by measuring antibody (immunoglobulin [Ig] M) titers against specific infectious agents, especially cytomegalovirus, Epstein–Barr virus, and *C. jejuni*. In selected cases, screening for HIV infection should be undertaken.

DIFFERENTIAL DIAGNOSIS

A number of well-defined conditions cause an acute or subacute onset of generalized weakness and must be differentiated from GBS (Table 175.2). These are disorders of the motor unit affecting the neuromuscular junction (e.g., myasthenia gravis and botulism), peripheral nerve (e.g., tick paralysis, shellfish poisoning, toxic neuropathy, acute intermittent porphyria, and diphtheritic neuropathy), motor neuron (e.g., amyotrophic lateral sclerosis, poliomyelitis, and West Nile virus [WNV] neuroinvasive disease), and muscle (e.g., periodic paralysis, metabolic myopathies, and inflammatory myopathies). Other conditions characterized by severe generalized weakness are defined by the setting in which they are encountered—the ICU—and are designated *critical illness polyneuropathy* and the *myopathy of intensive care*.

Intensive Care Unit–Related Weakness

Unlike neuromuscular emergencies such as GBS, myasthenia gravis, or porphyria, in which rapidly progressive weakness develops before admission to the ICU, a number of conditions (polyneuropathy, myopathy, and neuromuscular junction disease) affect patients already in the ICU because of severe systemic illnesses. These conditions are discussed in more detail in Chapter 180. Critical illness polyneuropathy is an axonal sensory-motor polyneuropathy characterized by difficulty weaning from the ventilator, distal greater than proximal muscle weakness, and reduced or absent reflexes that develop in patients with sepsis and multiorgan failure [26]. The development of weakness in the midst of critical illness, as seen in critical illness polyneuropathy, helps differentiate this disorder from axonal GBS, in which weakness develops days to weeks after an infection [27]. A severe necrotizing myopathy can also be seen in critically ill patients [28]. An acute myopathy of intensive care initially described in patients treated with a combination of high-dose corticosteroids (equal to or greater than 1,000 mg methylprednisolone) and neuromuscular blocking agents (NMBAs) for status asthmaticus [29] may also be encountered in the setting of trauma, organ transplantation, burns, and critical illness. Patients have variable degrees of generalized weakness, including respiratory muscles, and this is often recognized when a patient has difficulty weaning from the ventilator. Prolonged neuromuscular blockade after use of the nondepolarizing NMBAs can be seen especially in patients with coexistent renal failure and metabolic acidosis. Presumably, the presence of an active metabolite accounts for the prolonged weakness [30].

TABLE 175.2

CONDITIONS THAT MAY MIMIC GUILLAIN–BARRÉ SYNDROME

Disorder	Major distinguishing features
Myasthenia gravis	Reflexes are spared Ocular weakness predominates Positive response to edrophonium EMG: decremental motor response
Botulism	Predominant bulbar involvement Autonomic abnormalities (pupils) EMG: normal velocities, low amplitudes, incremental response (with high-frequency repetitive nerve stimulation)
Tick paralysis	Rapid progression (1–2 d) Tick present
Shellfish poisoning	Rapid onset (face, finger, toe numbness) Follows consumption of mussels/clams
Toxic neuropathies	EMG: usually axon loss
Organophosphorus	Acute cholinergic reaction toxicity
Porphyric neuropathy	Mental disturbance Abdominal pain
Diphtheritic neuropathy	Prior pharyngitis Slower evolution Palatal/accommodation paralysis Myocarditis
Poliomyelitis	Weakness, pain, and tenderness Preserved sensation Cerebrospinal fluid: protein and cell count elevated
West Nile virus neuroinvasive disease	Associated fever, meningitis, or encephalitis Asymmetric weakness Cerebrospinal fluid: protein and cell count elevated
Periodic paralysis	Reflexes normal Cranial nerves and respiration spared Abnormal serum potassium concentration
Critical illness neuropathy	Sepsis and multiorgan failure > 2 wk EMG: axon loss
Acute myopathy of intensive care	Tetraparesis and areflexia Follows prolonged treatment with neuromuscular-blocking agent and corticosteroids Trauma, status asthmaticus, and organ transplantation associated Clinical and EMG features of myopathy

EMG, electromyogram.

Disorders of the Neuromuscular Junction

In patients with myasthenia gravis, limb weakness is predominant proximally and almost always associated with ocular and sometimes pharyngeal muscle weakness (see Table 175.2; see Chapter 176). Muscular fatigability is a hallmark of the disease. Botulism may also cause acute weakness 6 to 36 hours after ingestion of the toxin formed by *Clostridium botulinum*. The condition is characterized by weakness of cranial nerve–innervated muscles, autonomic abnormalities (unreactive pupils and ileus), and occasional respiratory muscle weakness necessitating ventilator assistance.

Disorders of Peripheral Nerve

Tick paralysis is produced by a toxin contained in the head of the tick *Dermacentor andersoni* or *vanabilis* that blocks nerve conduction in the fine terminal portions of motor and sensory nerves. Weakness associated with sensory impairment develops rapidly after the tick has embedded itself into the victim, usually over 1 to 2 days. Shellfish poisoning gives rise to symptoms immediately after contaminated mussels or clams are eaten. Patients complain of face, finger, and toe numbness and then note the development of rapidly progressive descending paralysis, which may involve respiratory muscles.

Toxic neuropathies may be caused by a number of heavy metals, including arsenic, thallium, and lead. These and other potential neurotoxins (e.g., nitrofurantoin) and industrial agents (e.g., the hexacarbons) may produce a rapidly evolving peripheral neuropathy. Most acute toxic neuropathies are axon-loss in character, but in the case of arsenic poisoning, electrodiagnostic features may simulate a demyelinating process identical to some forms of GBS [31]. Organophosphorus insecticide toxicity causes a short-lived acute cholinergic phase marked by miosis, salivation, sweating, and fasciculation followed in 2 to 3 weeks by an acute axon-loss polyneuropathy [32]. An intermediate syndrome occurring 24 to 96 hours after the cholinergic phase and characterized by multiple cranial nerve palsies and respiratory failure has also been described [33]. The latter probably results from a defect at the neuromuscular junction.

Acute intermittent porphyria causes an acute polyneuropathy clinically similar to GBS but differing by its association with mental disturbance and abdominal pain. Attacks of paralysis are precipitated by ingestion of a variety of drugs, including alcohol, barbiturates, estrogens, phenytoin, and sulfonamides. The diagnosis may be established by demonstrating increased levels of porphobilinogen and δ-aminolevulinic acid in the urine.

Diphtheritic neuropathy occurs 2 to 8 weeks after a throat infection. During the height of the infection, there is numbness of the lips and paralysis of pharyngeal and laryngeal muscles. At the time of the neuropathy, diphtheria organisms may be cultured from the throat. Other clues to the diagnosis are clinical and electrocardiographic features of myocarditis.

Disorders of Motor Neurons

Amyotrophic lateral sclerosis is a chronic disorder of the motor system that generally evolves over several years to produce a state of severe generalized muscle weakness, atrophy, and fasciculations. In most instances, respiratory muscle weakness occurs in the latter stages of the illness after the diagnosis has been established. Rarely, however, patients present with acute to subacute respiratory muscle weakness (ventilatory failure) as the first clinical manifestation of this disease. The examination of such patients often discloses some features of lower motor neuron loss (muscle atrophy and fasciculations) in limb and bulbar muscles. The presence of brisk deep tendon reflexes and preserved sensation helps to distinguish this disorder from the neuropathies that might cause acute ventilatory failure. Unlike the situation in GBS where a picture of albuminocytologic dissociation is found, the CSF findings in amyotrophic lateral sclerosis are normal.

Poliomyelitis is rarely seen today, but it has developed in close contacts of newborns immunized with the live attenuated oral vaccine, and individuals whose own immunity to the virus has become inadequate. The disease is characterized by weakness of rapid onset along with severe muscle pain and tenderness. Respiratory muscles are often involved. Deep tendon reflexes are depressed. The illness is distinguished from GBS clinically by the preservation of sensation and the CSF findings. Serum antibody studies may help identify the illness.

A poliomyelitis-like syndrome may also be seen with WNV neuroinvasive disease. Infection of the anterior horn cells by the WNV produces an acute flaccid paralysis, with asymmetric weakness of one or more limbs, particularly the legs, along with hyporeflexia or areflexia. Overt sensory loss is typically absent while loss of bowel and bladder function may occur. Unlike GBS, there may be an associated meningitis, encephalitis, or fever in addition to CSF pleocytosis and elevated CSF protein. Diagnosis depends on detection of WNV-specific antibodies in serum or CSF [34].

Disorders of Muscles

Periodic paralysis (hyperkalemic or hypokalemic) is a disorder of muscle usually inherited in an autosomal-dominant fashion. Patients develop generalized weakness over a period of hours (see Table 175.2). Cranial nerve–supplied muscles are spared, there is generally no respiratory muscle involvement, reflexes are normal, and there is no sensory involvement. Serum potassium measurements aid in the diagnosis.

Rarely, metabolic myopathies may present with the sudden onset of muscle weakness. Patients with abnormalities of glycogen metabolism (e.g., phosphorylase deficiency) or lipid metabolism (e.g., carnitine palmityl transferase deficiency) may develop weakness associated with severe cramps and muscle fiber necrosis; the latter may result in creatine kinase elevations and myoglobinuria.

Dermatomyositis, an inflammatory myopathy, may present with the acute onset of proximal muscle (and, rarely, respiratory muscle) weakness. In contrast to the acute polyneuropathies, deep tendon reflexes are spared, cranial nerves are rarely involved, and serum creatine kinase is elevated.

PATHOGENESIS

AIDP is caused by immunologically mediated demyelination of the peripheral nervous system [3]. It is likely that humoral and cellular components of the immune system participate in macrophage-induced peripheral nerve demyelination [2,35]. Although the histological appearance of AIDP resembles experimental autoimmune neuritis, in which a predominantly T-cell–mediated immune response is directed against peripheral nerve myelin proteins, the role of T-cell–mediated immunity in AIDP remains unclear [35]. The finding of complement activation markers along the outer surface of the Schwann cell [36] have led to the speculation that complement-fixing antibodies directed toward as yet unidentified epitopes on the outer surface of the Schwann cell play a role in AIDP. Axonal degeneration may occur, especially in severe cases, as a "bystander" when there is intense inflammation [37,38].

In axonal subtypes, the immune response is targeted to a different portion of the peripheral nerve, the axon [39]. There is strong evidence that antibodies directed against ganglioside antigens on the axolemma target macrophages to invade the axon at the node of Ranvier [35]. The rapid decline and subsequent quick recovery in many AMAN patients suggests that severe axonal degeneration of the nerve roots is unlikely to be the pathological basis for this disorder; proposed mechanisms include physiological block of conduction or very distal degeneration and subsequent regeneration of the intramuscular motor nerve terminals [21].

The presence of antiganglioside antibodies (GM1 antibodies in both demyelinating and axonal GBS, and GD1 a, GM1b, and GalNAcGD1 a antibodies in axonal GBS) and the finding of ganglioside-like epitopes on some strains of *C. jejuni* have led to the concept of molecular mimicry [40], in which an immune attack occurs on the epitope shared by the nerve fiber and infectious organism [41], as a possible mechanism for GBS, especially *C. jejuni*–associated GBS. There is increasing evidence that anti-GM1 antibodies block sodium ion channels at the nodes of Ranvier, transiently producing conduction failure [42]. In addition, Koga et al. [43] found evidence that the genetic polymorphism of *C. jejuni* determines the production of specific autoantibodies and correlates with the clinical presentation of GBS, possibly through modification of the host-mimicking molecule.

PATHOLOGY

Pathologic studies of nerves in those patients dying with GBS have usually shown infiltration of the endoneurium by mononuclear cells, with a predilection for a perivenular distribution [37]. The inflammatory process occurs throughout the length of the nerve, from its origin at a root level to the distal ramifications of nerve twigs in the substance of muscle fibers. The brunt of the inflammatory process, however, occurs at more proximal levels (e.g., roots, spinal nerves, and major plexuses) and takes the form of discrete foci of inflammation. Macrophages invade intact myelin sheaths and denude the axons [35]. Patients with prominent axon loss are least likely to recover fully and may be left with functionally significant residual motor weakness.

In AMAN and AMSAN, there is evidence of Wallerian-like degeneration of nerve fibers, but only minimal inflammation or demyelination [25]. Macrophages are seen within the periaxonal space especially at the nodes of Ranvier, displacing or surrounding the axon, and leaving the myelin sheath intact [25]. Abnormalities are seen in nerve roots and peripheral nerves; in those with AMSAN, motor and sensory fibers are affected, while only motor fibers are affected in AMAN, with sparing of sensory fibers.

NATURAL HISTORY

The natural history of GBS in the moderately to severely affected patient (i.e., a patient who is unable to walk or who has severe respiratory muscle weakness requiring a ventilator) is usually one of gradual improvement. The ability to walk unassisted returns, on average, in approximately 3 months; in the subset of respirator-dependent patients, the average time to recovery is 6 months [44].

MANAGEMENT

The three major treatment issues in GBS are controlling respiration and deciding when to intubate the patient, recognizing and managing autonomic dysfunction, and determining which patients are candidates for plasmapheresis or intravenous immunoglobulin (IVIG) (Table 175.3).

TABLE 175.3

MANAGEMENT OF GUILLAIN–BARRÉ SYNDROME

General	Monitor respiratory parameters: VC, arterial blood gas Intubate if: VC < 12–15 mL/kg Oropharyngeal paresis with aspiration Falling vital capacity over 4–6 h Respiratory fatigue with VC 15 mL/kg Use short-acting medications to control autonomic dysfunction Nursing care: frequent turns to avoid pressure sores Place pads at elbows and fibular head to avoid compression neuropathies Physical therapy Subcutaneous heparin
Treatment:	
Plasmapheresis	Exchange a total of 200 mL plasma/kg body weight over 7–14 d (40–50 mL/kg for 3–5 sessions)[a] Albumin is used as replacement solution, not fresh-frozen plasma During plasmapheresis, monitor blood pressure and pulse every 30 min Obtain complete blood cell count (baseline and before each exchange to calculate plasma volume) Obtain immunoglobulin levels before first exchange and after last exchange; if immunoglobulin G < 200 mg/dL after last plasma exchange, infuse 400 mg/kg IVIG
IVIG	2 g/kg divided over 5 consecutive d[b] (0.4 g/kg/d for 5 d)

[a]This is the authors' approach, following the Guillain–Barré Syndrome Study Group guidelines [44]. Other published guidelines recommend two sessions (exchanging 40 mL/kg per session) for ambulatory patients and four sessions (exchanging 40 mL/kg per session) for nonambulatory patients [53].
[b]The authors adhere to the protocol published by the Dutch Guillain–Barré Study Group [54].
IVIG, intravenous immunoglobulin; VC, vital capacity.

Patients with GBS require excellent nursing care, medical management, and emotional support. Respiratory failure is one of the most serious complications of GBS. Need for a ventilator cannot be reliably predicted on the basis of extent of weakness; however, patients who are highly likely to require mechanical ventilation are those with rapid disease progression, bulbar weakness, autonomic dysfunction, and bilateral facial weakness [45]. Patients must be followed carefully with measurements of maximum inspiratory pressure and forced vital capacity (FVC) (Fig. 175.1) until weakness has stopped progressing so the respiratory insufficiency can be anticipated and managed appropriately. A normal FVC is 65 mL per kg; a level of 30 mL per kg is generally associated with a poor forced cough and requires careful observation and management with supplemental oxygen and chest physical therapy. At 25 mL per kg, the sigh mechanism is compromised and atelectasis occurs, leading to hypoxemia. Ropper and Kehne [46] suggest intubation

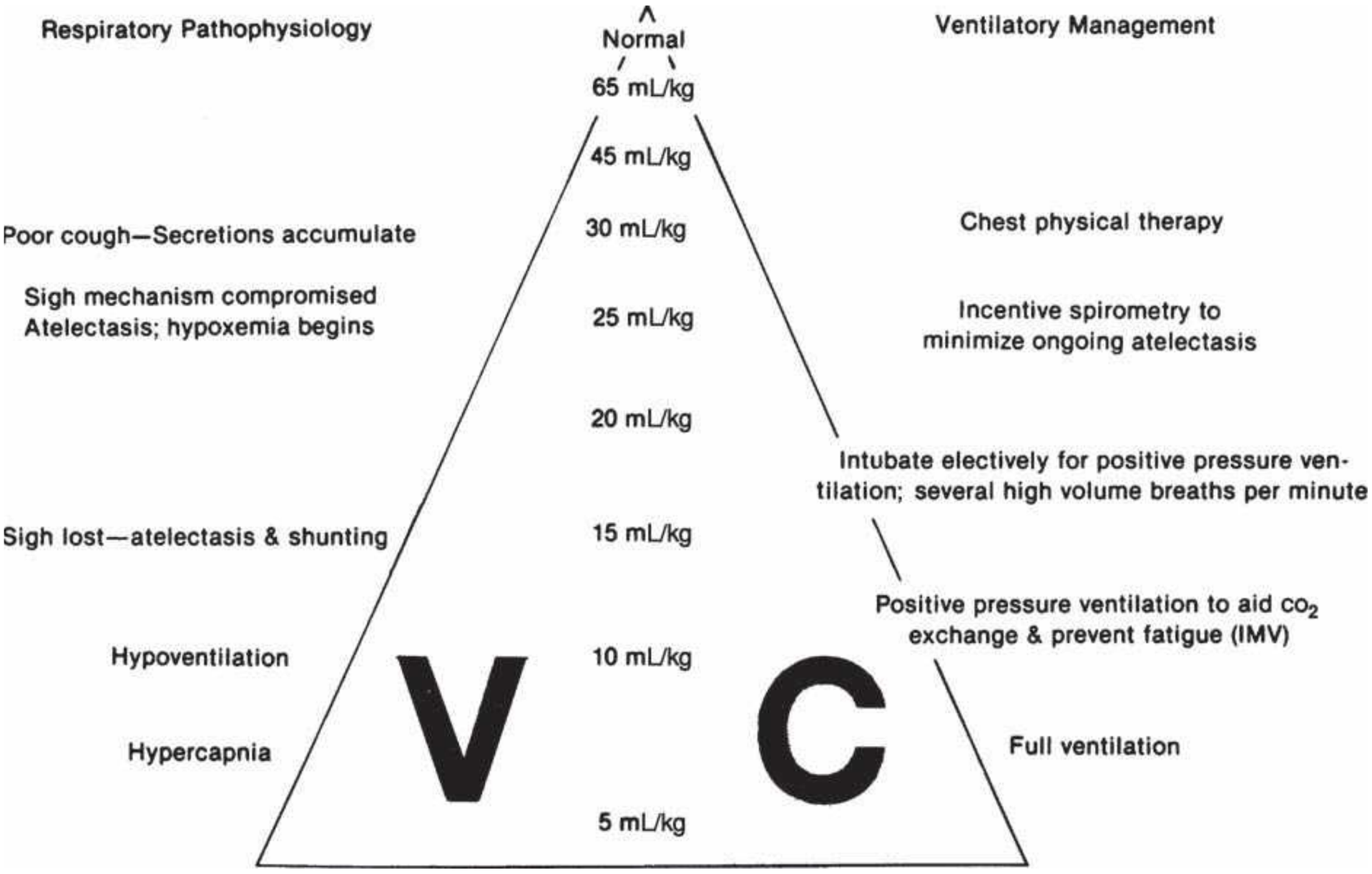

FIGURE 175.1. Relations between vital capacity (VC), pathophysiology of lung function, and suggested therapy in mechanical ventilatory failure. IMV, intermittent mandatory ventilation. [From Ropper AH: Guillain-Barré syndrome, in Ropper AH, Kennedy SK, Zervas NT (eds): *Neurological and Neurosurgical Intensive Care*. Baltimore, University Park Press, 1983, with permission.]

if any one of the following criteria is met: mechanical ventilatory failure with reduced expiratory vital capacity (VC) of 12 to 15 mL per kg, oropharyngeal paresis with aspiration, falling VC over 4 to 6 hours, or clinical signs of respiratory fatigue at a VC of 15 mL per kg. Lawn et al. [45] found the following respiratory factors to be highly associated with progression to respiratory failure: VC less than 20 mL per kg, maximal inspiratory pressure (MIP) less than 30 cm H_2O, maximal expiratory pressure (MEP) less than 40 cm H_2O, or a reduction of more than 30% of VC, MIP, or MEP in 24 hours. Elective intubation may be considered in these patients at particularly high risk for progression to respiratory failure. Intubation should be accomplished with a soft-cuff low-pressure endotracheal tube. A decision to delay tracheostomy for 7 to 10 days is likely to avoid the operation in as many as one-third of patients who improve rapidly and can be extubated after the first few days [46]. Complications of intubation and ventilator assistance are described in Chapters 1 and 58.

The nursing and medical team must also be aware of the many autonomic nervous system disturbances that can occur [18]. Fluctuating blood pressure with transient hypertensive episodes, sometimes associated with extreme degrees of agitation, may be present. Other manifestations of sympathetic nervous system overactivity include sudden diaphoresis, general vasoconstriction, and sinus tachycardia. Evidence of underactivity of the sympathetic nervous system includes presence of marked postural hypotension and heightened sensitivity to dehydration and sedative-hypnotic agents. Excessive parasympathetic nervous system activity is reflected in facial flushing associated with a feeling of generalized warmth and bradycardia. Electrocardiographic changes, consisting of ST- and T-wave changes, also occur. Therefore, careful monitoring of blood pressure, fluid status, and cardiac rhythm is absolutely essential to manage the GBS patient. Hypertension may be managed with short-acting α-adrenergic blocking agents, hypotension with fluids, and bradyarrhythmias with atropine [18]. As noted earlier, hyponatremia may occur and is probably best managed by fluid restriction.

The bedridden patient needs to be turned frequently to avoid the development of pressure sores. Paralyzed limbs require the attention of the physiotherapist so that passive limb movements can be carried out and contractures prevented. The treatment team needs to be aware of the potential for development of compression neuropathies (most commonly of the ulnar and peroneal nerves), and insulating pads should be placed over the usual susceptible sites (the elbow and the head of the fibula). Pain may be treated with standard doses of analgesic agents, but they do not often provide adequate relief. Gabapentin or carbamazepine is particularly helpful in treating the pain in the acute phase [47] and, when disabling, epidural morphine may be necessary [48]. Deep venous thrombosis and pulmonary embolism are ever-present dangers in the bedridden patient with immobilized limbs; for these patients, in addition to physical therapy, subcutaneous heparin (5,000 U twice per day) and support stockings are recommended [47].

A number of multicenter studies [44,49,50] showed that plasmapheresis has a beneficial effect on the course of the illness, even in those patients with several poor prognostic signs [51]. Patients treated with plasmapheresis are able to walk, on average, 1 month earlier than untreated patients; respirator-dependent patients so treated walk 3 months sooner than those who do not receive plasma exchange [44]. The GBS study group guidelines recommend exchanging 200 to 250 mL plasma per kg body weight over 7 to 14 days in three to five treatments [44]. Five percent salt-poor albumin is used as replacement fluid (fresh-frozen plasma should be avoided because of risks

of hepatitis, HIV, and occasionally pulmonary edema). It is important to keep in mind, however, that there are also possible risks with albumin, including bleeding, thrombosis, and infection (due to loss of coagulating factors and γ-globulins during plasma exchange, which are not present in the albumin replacement fluid). After each exchange, γ-globulin can be infused to prevent infection.

Plasmapheresis, in general, is recommended for patients who have reached or are approaching the inability to walk unaided, who require intubation or demonstrate a falling VC, and who have weakness of the bulbar musculature leading to dysphagia and aspiration [52]. The French Cooperative Group on Plasma Exchange in Guillain–Barré Syndrome [53] also showed that treatment of patients with mild GBS (i.e., those who are still ambulatory) is beneficial; two plasma exchanges were more beneficial than none in time to onset of motor recovery in patients with mild GBS. Patients with moderate (not ambulatory) or severe (mechanically ventilated) GBS benefited from four exchanges; those with severe GBS did not benefit any further with the addition of two more exchanges. Because of its potential for inducing hypotension, patients who have compromise of their cardiovascular system or autonomic dysfunction may not tolerate this procedure. Plasmapheresis is safe in pregnant women and children [4]. Plasmapheresis is generally not used in patients who are no longer progressing 21 days or more after the onset of GBS.

For many years, plasmapheresis was the gold standard in the treatment of GBS. In 1992, a large randomized trial performed by Dutch investigators demonstrated that treatment with IVIG was at least as effective as plasmapheresis and might be superior [54]. A subsequent large randomized controlled trial (the Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group) confirmed the equivalence of IVIG and plasma exchange; in addition, there was no substantial benefit in using a combination of plasma exchange followed by IVIG [55]. In light of these studies, plasma exchange or IVIG may be used to treat GBS. Although both treatments are equally efficacious, IVIG has become the preferred treatment because of its relative ease of administration (plasmapheresis is not available in all centers, and it requires good venous access and a stable cardiovascular system). In 3% to 12% of patients given IVIG, side effects may occur that range from minor reactions such as flulike symptoms, headache, nausea, and malaise to more severe side effects, including anaphylactic reactions in IgA-deficient persons, transmission of hepatitis C, aseptic meningitis, and acute renal failure in those with renal insufficiency. Absolute contraindications to IVIG are unusual, however. For example, patients with IgA deficiency may be given an IgA-poor preparation with precautions (can be pretreated with Benadryl or Tylenol), whereas those with renal insufficiency may be given an IVIG sucrose-poor preparation with close monitoring of their renal status.

A recent American Academy of Neurology practice parameter recommends treatment of GBS patients who are unable to walk with either plasmapheresis or IVIG; treatment is beneficial if given within 4 weeks of onset of neuropathic symptoms for plasmapheresis and within 2 weeks (and possibly 4 weeks) of onset for IVIG [56]. For those patients who are still ambulatory, plasmapheresis may also be considered if given within 2 weeks of onset. Treatment with plasmapheresis followed by IVIG is not recommended.

In a small number of patients (5%), spontaneous relapse occurs within days to weeks after treatment with IVIG or plasmapheresis, oftentimes in those treated early in their illness. Relapse rates are similar in frequency between IVIG and plasmapheresis [57]. Although retreatment with the same therapy is commonly practiced [58], generally with half the initial dose used [59], evidence-based literature is lacking regarding the efficacy of repeat treatment [57].

Although it seems intuitively obvious that treatment of GBS with corticosteroids should be beneficial, corticosteroids are generally ineffective. Hughes and colleagues [60] reviewed six randomized trials of corticosteroid use for GBS; they found no significant difference in disability-related outcome between corticosteroid and placebo groups. Oral corticosteroids delayed recovery while IV methylprednisolone alone was not beneficial or harmful [60]. Although the combination of IVIG and IV methylprednisolone (500 mg per day for 5 days) showed no significant difference over IVIG alone unless adjusted for various factors, there is a trend toward shortened time to independent ambulation with combination treatment [58,61]. Corticosteroids are not recommended in the treatment of GBS.

Finally, it is most important to address the emotional needs of the patient with GBS, who will almost certainly be anxious, fearful, and depressed. The strong likelihood of a good outcome, even in ventilated patients, is noted later in this chapter. Sometimes it is helpful for the patient to speak with a person who has recovered from GBS.

OUTCOME AND PROGNOSTIC FACTORS

In most patients recovery occurs over weeks or months, but in some patients, muscle strength may take 1.5 to 2.0 years to reach its best state with an intensive rehabilitation program [2]. Recovery is not always complete, with only approximately 15% of patients resolving with no residual deficits [4]. Another 50% to 65% of patients are restored to nearly normal function and can resume their work and leisure activities, although some degree of ankle dorsiflexor weakness or numbness of the feet is commonly encountered. Many patients never regain normal stretch reflexes. Severe residual motor weakness or major proprioceptive loss that seriously impairs walking occurs in approximately 10% of patients. Despite close monitoring in the ICU, deaths from GBS do occur, with mortality in the range of 3% to 8% [4]. Causes of fatal outcomes include dysautonomia, sepsis, acute respiratory distress syndrome, and pulmonary emboli [4].

Poor prognostic factors include older age (≥ 50 years), severe disease at nadir (bedbound or requiring mechanical ventilation), rapid onset of disease, and evidence of axonal loss (reflected on electrodiagnostic studies) [35,42,62]. More recently, elevated CSF neurofilament levels predicted poor outcome, presumably reflecting axonal damage of the proximal motor nerve root [63].

SUMMARY

Careful attention to the patient's history and thorough examination usually point to the diagnosis of GBS, which may be corroborated by the CSF findings (i.e., albuminocytologic dissociation) and results of electrophysiologic testing (i.e., acquired demyelinating or axon-loss polyneuropathy). The mainstay of treatment is excellent nursing and medical care, with close attention to respiratory and autonomic function. Although 10% of patients with GBS are left with substantial residual neurologic deficits, the majority improve and resume their premorbid lifestyles; plasmapheresis and IVIG have been shown to enhance recovery.

Advances in the management of GBS, based on randomized controlled trials or meta-analyses of such trials, are summarized in Table 175.4.

TABLE 175.4

ADVANCES IN MANAGEMENT BASED ON MAJOR CONTROLLED CLINICAL TRIALS OF PLASMAPHERESIS AND INTRAVENOUS IMMUNOGLOBULIN IN GUILLAIN–BARRÉ SYNDROME

References	Purpose	Results
44	Compared PE with supportive care	PE showed beneficial effect in time to improve one clinical grade, time to independent walking, and outcome.
53	Compared various PE treatment schedules in three severity groups	Mild group: 2 PEs more effective than none. Moderate group: 4 PEs more effective than 2 PEs. Severe group: 6 PEs not more beneficial than 4 PEs.
50	(a) To determine effect of PE initiated within 17 d onset and (b) to compare albumin and FFP as replacement fluids	PE beneficial when administered early. No significant difference between albumin and FFP but albumin preferred due to less risks.
54	To determine whether IVIG is as effective as PE	IVIG is as effective as PE and may be superior.
55	Compared IVIG with PE, and combined regimen of PE followed by IVIG	PE and IVIG are equivalent in efficacy when treatment is given within the first 2 weeks of symptoms. The combination of PE followed by IVIG was not more beneficial.

IVIG, intravenous immunoglobulin; FFP, fresh-frozen plasma; PE, plasmapheresis.

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CHAPTER 176 ■ MYASTHENIA GRAVIS IN THE INTENSIVE CARE UNIT

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Few physicians have more than a passing acquaintance with myasthenia gravis, although it is by no means rare. The key to handling the emergent problems associated with myasthenia is simply the management of airway and ventilatory support with the same care as in any other instance of respiratory failure (see Chapters 1, 58, and 59). With respiration under control, the treatment of the underlying disease can be unhurried and orderly, and in most patients, it is successful. This chapter reviews briefly the pathogenesis, clinical spectrum, and diagnosis of myasthenia gravis and focuses on the intensive care setting, including management of the patient in crisis and in the perioperative period.

PATHOGENESIS

Myasthenia gravis is an autoimmune disorder of neuromuscular transmission [1]. Circulating antibodies react with components of acetylcholine receptors within postsynaptic muscle membrane and activate complement-mediated lysis of the muscle membrane, accelerate receptor degradation, and block receptors (i.e., interfere with normal receptor activation by acetylcholine) [2]. The result is fewer receptors that can be activated at affected neuromuscular junctions, causing weaker muscular contraction. Electrophysiologic study of myasthenic neuromuscular junctions discloses miniature end-plate potentials that are diminished in amplitude [3]. These observations have been clearly linked to the receptor alterations and an altered postsynaptic response to normal quantal transmitter release from the presynaptic nerve terminals. Understanding of this underlying pathophysiology has, in turn, enabled rational approaches to treatment. Various immunosuppressive therapies and acetylcholinesterase inhibitors are primary therapeutic options in managing myasthenia gravis (see later).

EPIDEMIOLOGY

Myasthenia gravis is not rare; its prevalence in Western populations is approximately 1 in 20,000 [4]. The overall female to male ratio is approximately 3:2, although there are two distinct sex-specific incidence peaks, with the incidence among women peaking in the third decade and that among men in the fifth to sixth decades. A mild familial predisposition has been noted, although Mendelian inheritance does not apply.

CLINICAL SPECTRUM

The clinical spectrum of myasthenia gravis is characterized as much by its diversity as it is by its common themes. It may range from a mild and relatively inconsequential disease over a normal lifetime to a fulminant incapacitating disorder. The course of given individuals may also vary widely. The clinical hallmarks of the disease are weakness and exaggerated muscle fatigue. The specific muscles involved and the severity of weakness are highly variable, between individuals and within the same individual over time.

Ocular muscles are most frequently involved; diplopia is common, and various patterns of ophthalmoparesis are seen.

Bulbar muscles are also frequently affected, leading to varying combinations of facial paresis, dysarthria, and dysphagia. Ptosis is common, but the pupils are never affected. Limb muscle involvement may vary from very isolated weakness to generalized (usually proximal) weakness and fatigability. Respiratory muscle weakness is unfortunately not rare, and respiratory insufficiency and the inability to handle oral and upper airway secretions are the critical problems that bring myasthenics to the intensive care setting. Myasthenia should also be considered in any patient who cannot be weaned from ventilator support after an otherwise uncomplicated surgical procedure.

Approximately 15% to 20% of myasthenics have only ocular and eyelid involvement. Longitudinal studies indicate that if an individual manifests only oculomotor weakness for more than 2 years, there is little chance of later limb or respiratory weakness. Although several clinical classification schemes have been devised for categorizing myasthenics according to the distribution and severity of their disease, it is preferable to emphasize the fact that myasthenics often fluctuate over time, with variability rather than constancy being the norm. Some factors contributing to fluctuations of strength are recognizable (see later); many fluctuations appear to be random occurrences.

DIAGNOSTIC STUDIES

The diagnosis of myasthenia gravis is clinically suggested in patients who present with chronic ocular, bulbar, or appendicular weakness, variable over time, with preservation of normal sensation and reflexes. More restricted presentations require a much broader differential diagnosis. Myasthenia gravis should always be considered in the differential diagnosis of isolated ocular or bulbar weakness. Again, prominent muscular fatigability and temporal fluctuation are key features of the disease. Normal pupils, normal sensation, and normal reflexes are to be expected and are helpful in diagnosing myasthenia gravis when coincident with an acute or subacute paralytic illness.

Once the diagnosis of myasthenia gravis is suggested, confirmation rests on the exclusion of other diseases and supporting clinical and laboratory studies. It is important to stress that although abnormal tests may be diagnostic, normal test results do not exclude the diagnosis.

Edrophonium Test

Edrophonium hydrochloride (Enlon; formerly "Tensilon") is a fast, short-acting parenteral cholinesterase inhibitor. It reaches peak effect within 1 minute after intravenous injection and persists to some extent for at least 10 minutes. Myasthenic weakness typically improves transiently after administration of 4 to 10 mg (0.4 to 1.0 mL). The edrophonium test may be blinded, with drug or normal saline being injected. Whether drug or placebo, a 0.2-mL test dose is given to screen for excessive cholinergic side effects, such as cardiac arrhythmia, gastrointestinal hyperactivity, or diaphoresis. A crash cart should always be available, and patients with known cardiac disease and elderly patients warrant electrocardiographic monitoring. The remaining 0.8 mL is given after 1 minute. Interpretation of the test depends on identifying and observing an unequivocal baseline muscular deficit that can be improved following the injection of edrophonium. Ptosis and ophthalmoparesis, if present, are semiquantifiable and well suited; if respiratory compromise is present, monitoring maximum inspiratory pressure (MIP) or vital capacity is useful. As a general rule, positive responses are dramatic; if there is any doubt about the positivity of the test, it should be considered negative. False-positive edrophonium tests are quite rare; false negatives are common. In children, the appropriate test dose is 0.03 mg per kg, one-fifth of which may be given as a test dose.

Neostigmine is a longer-acting parenteral cholinesterase inhibitor that sometimes affects a more obvious clinical response. It is also typically associated with more obvious autonomic side effects. The 1.5-mg test dose (0.04 mg per kg in children) should therefore be preceded by 0.5 mg of atropine; both may be given subcutaneously.

Serological Testing

Recognition of the immune nature of myasthenia gravis has provided a relatively sensitive and highly specific diagnostic study. Approximately 85% of myasthenics have detectable serum antibodies, which bind to acetylcholine receptors (AChR) [5]. The sensitivity drops to 70% in those with purely ocular myasthenia [6]. The antibodies themselves constitute a heterogeneous group, reacting against various receptor subunits. Although the actual antibody titer is of little significance, correlating poorly with the severity of disease or clinical response to therapy, the presence of antibodies is a strong indication of the disease. A normal test does not exclude the diagnosis, especially in the patient presenting with predominantly ocular symptoms and signs. Of note, these antibodies have also been found in a small percentage of patients with Lambert–Eaton myasthenic syndrome, autoimmune liver disorder, and patients with lung cancer without neurologic disease [6].

Among seronegative myasthenic patients, from 30% to 70% may be found to have antibodies directed against muscle-specific tyrosine kinase [MuSK], an enzyme that catalyzes acetylcholine receptor aggregation in the formation of neuromuscular junctions [7]. Animal models have also recently shown that MuSK antibodies may reduce acetylcholine receptor clustering and thus impair neuromuscular transmission [8]. Patients who have antibodies to MuSK are often young women (onset of symptoms before 40 years of age) with prominent bulbar involvement [9] and neck or respiratory muscle weakness [7]. They tend to have more severe disease requiring aggressive immunosuppressive treatment [9] and have a higher frequency of respiratory crisis compared to seronegative or AChR-positive myasthenics [10]. Unlike patients with antibodies to AChR, there appears to be a correlation between MuSK antibody levels and disease severity, with antibody levels often decreasing after various immunosuppressive treatments except thymectomy [11].

Striated muscle antibodies that react with muscle proteins titin and ryanodine receptor have also been found, mainly in patients with thymoma and in those with late onset myasthenia (onset of symptoms > 50 years of age) [12]. Thus, they may be helpful in the detection or recurrence of thymoma. In addition, they tend to be associated with more severe disease, and therefore may aid in prognosis [12].

Myasthenics also have an increased incidence of other autoantibodies, including antithyroid antibodies, antiparietal cell antibodies, and antinuclear antibodies, although routine screening for these is not part of the diagnostic evaluation for suspected myasthenia gravis.

Electromyographic Studies

The electromyographic hallmark of myasthenia gravis is a decrement in the amplitude of the muscle potential seen after exercise or slow repetitive nerve stimulation. The decrement should be at least 10% and preferably 15% or more. Routine motor and sensory conduction studies are normal, as is the conventional needle examination. The more severely

affected patient is more likely to show a decremental response; responses are most consistently elicited from facial and proximal muscles. If a significant decrement is observed, exercising the muscle briefly for 10 seconds transiently reverses the decrement [13]. Single-fiber electromyography is relatively sensitive, documenting increased jitter [14]—variability in the temporal coupling of single fibers within the same motor unit. Increased jitter, however, is far from specific; most peripheral neurogenic diseases also lead to increased jitter.

MISCELLANEOUS STUDIES

Myasthenia gravis may be associated with either malignant thymoma or thymic hyperplasia. Once a diagnosis is established, chest imaging should be obtained. Because there is also a significant association with thyroid and other autoimmune diseases, appropriate screening studies are indicated in the newly diagnosed myasthenic. Muscle biopsy has no role in the evaluation of myasthenia, unless there is a strong consideration of neurogenic or inflammatory weakness.

CRITICAL CARE OF THE MYASTHENIC PATIENT

Patient in Crisis

Crisis refers to threatened or actual respiratory compromise in a myasthenic patient. It may reflect respiratory muscle insufficiency or inability to handle secretions and oral intake, but it is typically a combination of both. With currently available treatments, myasthenic crisis is not common. An occasional patient presents with fulminating disease; crisis management then coincides with initial evaluation and institution of therapy. Otherwise, crisis may be precipitated by other illnesses, such as influenza or other infections, or by surgery.

General Measures

The respiratory function of any acutely deteriorating or severely weak myasthenic should be monitored compulsively. When the weakening myasthenic reaches a point at which increased respiratory effort is required, fatigue often prevents the effective use of secondary muscles, and respiratory failure rapidly ensues. Arterial blood gas values and even oxygen saturation are poor indicators of incipient failure in the face of respiratory muscle compromise. Forced vital capacity (FVC) and MIP are better indices and should be serially charted. The FVC should be assessed with the patient both sitting and supine, because diaphragmatic paresis may be accentuated in the supine position. MIP measurement requires special care if the patient also has significant facial weakness. An FVC less than 20 mL per kg or an MIP greater than (i.e., not as negative as) −40 cm H_2O suggests impending failure and usually warrants intubation. If a downward trend is noted (greater than 30% decrease) [15], elective intubation should be considered even sooner, unless there is a realistic expectation of rapid reversal.

Acute deterioration in a myasthenic always warrants consideration of contributing circumstances or concurrent illness that may accentuate the underlying defect in neuromuscular transmission. The major considerations are listed in Table 176.1 and discussed later.

The possibility of cholinergic crisis in patients receiving anticholinesterase drugs (e.g., pyridostigmine), although no longer common, should not be overlooked. The presence of fasciculations, diaphoresis, or diarrhea should alert the clinician to this possibility. In the past, the importance of differentiating between myasthenic crisis and cholinergic crisis was stressed. Edrophonium testing was used to differentiate between the two; abrupt deterioration after a conventional 10-mg test dose indicated overdosage with cholinesterase inhibitors. One had to be adequately prepared for deterioration and increased respiratory secretions. Because oftentimes it is very difficult to determine the response and because of the potential side effects with overdosage of anticholinesterase drugs of increased pulmonary secretions, many authors now recommend discontinuation of cholinesterase inhibitors at the time of crisis [2,16,17] and reinstituting them when patients are stronger. This assumes that adequate respiratory monitoring and support are in effect. A brief holiday from cholinesterase inhibition also often results in an enhanced response to therapy when reinstituted.

TABLE 176.1

CONDITIONS THAT MAY UNDERLIE INTERIM DETERIORATION IN MYASTHENIC PATIENTS

Intercurrent infection; occult infection should be excluded
Electrolyte imbalance (Na, K, Ca, P, Mg)
Cholinergic crisis: if any doubt, discontinue cholinesterase inhibitors
Thyrotoxicosis, hypothyroidism
Medication effects (see Table 176.2)

Intercurrent infection is often associated with increased weakness in the myasthenic patient. There should be a comprehensive search for systemic infection in the deteriorating patient, particularly the patient receiving immunosuppressive therapy. Any infections should be treated aggressively. Both hypothyroid and hyperthyroid states are often associated with increased weakness. Again, there is an increased association between thyrotoxicosis and myasthenia gravis. The manifestations of electrolyte imbalance may be enhanced in myasthenics. Otherwise, insignificant electrolyte effects on transmitter release or muscle membrane excitability may be amplified at the myasthenic neuromuscular junction. Potassium, calcium, phosphate, and magnesium alterations should be corrected. Myasthenia gravis may also impart enhanced sensitivity to a number of medications that have only minimal effects on neuromuscular function in normal individuals. Aminoglycoside antibiotics, beta-blockers, and many cardiac antiarrhythmics may have adverse effects. Anticholinergics, respiratory depressants, and sedatives of any kind should be avoided or used only with great caution. *Neuromuscular-blocking agents should never be administered to myasthenics in the intensive care unit (ICU) setting*, because they often have profound and prolonged effects. This increased sensitivity occasionally results in postoperative failure to wean in an undiagnosed mild myasthenic who has undergone surgery for an unrelated problem. Table 176.2 provides a comprehensive listing of medications that may further impair neuromuscular transmission in myasthenic patients.

Some attention should also be given to the general environment in which the myasthenic is managed. The typical noisy, brightly illuminated ICU is not conducive to rest and sleep, which are necessities for the myasthenic patient in whom fatigue may be critical.

Special consideration must be given to respiratory care of the myasthenic. Incentive spirometry should be avoided, because muscular fatigue outweighs any potential benefit, even in the postoperative patient. Careful attention to respiratory toilet is key and can be complicated by cholinesterase inhibitors, which increase respiratory secretions. Atropine may be used to minimize this effect, but its other autonomic side effects, such as ileus, constipation, and delirium, may limit longer-term use.

TABLE 176.2

MEDICATIONS THAT MAY ACCENTUATE WEAKNESS IN MYASTHENIC PATIENTS

Antibiotics	Neuromuscular blockers and muscle relaxants	Antiarrhythmics and antihypertensives	Antirheumatics	Antipsychotics	Others
Amikacin	Anectine (succinylcholine)	Lidocaine	Chloroquine	Lithium	Opiate analgesics
Clindamycin	Norcuron (vecuronium)	Quinidine	d-Penicillamine	Phenothiazines	Oral contraceptives
Colistin	Pavulon (pancuronium)	Procainamide		Antidepressants	Antihistamines
Gentamicin	Tracrium (atracurium)	Beta-blockers			Anticholinergics
Kanamycin	Benzodiazepines	Calcium blockers			
Lincomycin	Curare				
Neomycin	Dantrium (dantrolene)				
Polymyxin	Flexeril (cyclobenzaprine)				
Streptomycin	Lioresal (baclofen)				
Tobramycin	Robaxin (methocarbamol)				
Tetracyclines	Soma (carisoprodol)				
Trimethoprim/ sulfamethoxazole	Quinamm (quinine sulfate)				

THERAPY IN MYASTHENIC CRISIS

Therapeutic agents used in the critical care setting parallel those available to the patient with milder myasthenia gravis. Immunosuppressive therapies are the major considerations. Any myasthenic in crisis, if not already receiving immunosuppressive therapy, requires it. Symptomatic therapy with cholinesterase inhibitors is now primarily used on a shorter-term basis, pending response to immunomodulating therapies. Plasmapheresis, intravenous human immune globulin, corticosteroids, and longer-term immunosuppressants and cholinesterase inhibitors are discussed individually.

Plasmapheresis

Recognition of the role of immunoglobulins in the pathogenesis of myasthenia gravis stimulated early, uncontrolled clinical trials of plasmapheresis as soon as efficient pheresis technology became available [18]. The results have been quite favorable, prompting the National Institutes of Health Consensus Conference to support its use despite the lack of controlled trials [19]. Most patients demonstrate a significant clinical response within 48 hours of initiation of plasmapheresis, although the response is short lived unless therapy is continued on an intermittent basis. The rapid response from plasmapheresis can be crucial in the face of crisis, providing a short-term reprieve during which alternative therapy can be initiated or any intercurrent medical problems resolved. Approximately 50 mL per kg should be exchanged per session [20], approximating 60% to 70% of total plasma volume. Plasma removed is replaced by an equal volume of normal saline and 5% albumin, adjusted to maintain physiologic concentrations of potassium, calcium, and magnesium. The usual course of treatment includes three to seven pheresis sessions at 24- to 48-hour intervals. Many patients develop increased sensitivity to cholinesterase inhibitors after plasmapheresis; dosage should be correspondingly reduced. The major potential complications of plasmapheresis include hypotension, arrhythmia, and hypercoagulability due to hemoconcentration. Coincident cardiovascular disease is a relative contraindication to plasmapheresis. Although plasmapheresis is too invasive to be used for long-term therapy in the majority of patients, periodic plasmapheresis has been beneficial in some patients with moderate to severe myasthenia refractory to immunosuppressive agents [21]. Selective removal of acetylcholine receptor antibodies using immunoadsorption columns may also be a promising alternative to plasmapheresis, but further clinical studies are required [22].

Intravenous human immune globulin also frequently leads to rapid yet transient improvement in myasthenics [23]. Intravenous immunoglobulin (IVIG) is a therapeutic option in the event of crisis or in the perioperative period, particularly if the patient's cardiovascular status limits plasmapheresis. Although IVIG and plasmapheresis were found to be equally efficacious in some trials [24], others have reported that plasmapheresis was more efficacious than IVIG; however, complications occurred more often with plasmapheresis [25]. The customary dose is 400 mg per kg per day for 5 consecutive days. More recently, a total dose of 1 gram per kilogram was reported to be equally efficacious to 2 gram per kilogram, although there was a trend toward slight superiority of the higher dose [26]. Maximal improvement occurs by the second week after therapy, and the therapeutic response usually persists for several weeks. Patients should be pretreated with acetaminophen and diphenhydramine to prevent flu-like symptoms that commonly occur during infusion. In addition, adequate hydration will help reduce the potential complication of thrombosis. Renal function should be checked prior to initiation of therapy, as renal failure may occur in those with renal insufficiency. Likewise, an IgA level should be obtained as patients with IgA deficiency may develop anaphylaxis.

Longer-Term Immunosuppression

Corticosteroids have proven to be an effective long-term therapy for almost all myasthenics whose clinical manifestations cannot be well managed with low doses of cholinesterase inhibitors. Despite potential side effects associated with corticosteroid therapy, a response rate of greater than 80% supports its use [27]. Side effects can be minimized with appropriate precautions. Carbohydrate metabolism, electrolytes, blood pressure, and diet should be closely monitored; bisphosphonates (e.g., alendronate sodium, 70 mg weekly), calcium (500 to 1,000 mg per day), and vitamin D supplementation (at least 800 to 1,000 IU per day) as well are prudent to minimize osteopenia. Screening for tuberculosis exposure with skin testing and chest radiographs should be done before initiation of therapy. Occult infection must be excluded in the deteriorating myasthenic.

Recommendations regarding corticosteroid preparation, dose, and regimen vary. Approximately one-third of patients may become transiently weaker before they improve, if given high doses of prednisone initially [3]. Initiation with relatively low doses of prednisone and increasing in a stepwise manner has been advocated by some clinicians to minimize interim deterioration, especially if the patient is not intubated [16]. The authors prefer to begin with 15 to 25 mg of prednisone or its equivalent as a single daily dose, increasing the dose by 5 mg every second or third day until a dose of 1 mg per kg per day is reached. In the critical care setting, concurrent plasmapheresis or IVIG may offset initial steroid-related deterioration; high doses of corticosteroids (1 mg per kg per day) can be initiated in this situation, enabling a more rapid response. Oral corticosteroids are preferable since there is a risk of developing acute steroid-induced myopathy in patients with myasthenia who are given high doses of intravenous corticosteroids [17,28].

Once maximal response is obtained, usually within 1 to 2 months, patients may be gradually shifted to alternate-day therapy by concurrently reducing the off-day dose and increasing the on-day dose, with a 10-mg shift made once each week. Some individuals note a definite off-day adverse effect; this can usually be countered with a 10-mg alternate-day dose. Once stabilized on alternate-day therapy, the on-day dose can be tapered by 5 mg per month. Many patients can be maintained in remission with as little as 20 to 25 mg of prednisone every other day (or alternating with 10 mg). Only rare patients remain in remission if therapy is discontinued, and overenthusiastic tapering of steroids is an all too common precipitant of unnecessary disability or even crisis. Myasthenia sometimes remits spontaneously, and if the patient has undergone thymectomy (see later), the probability of remission increases appreciably, making discontinuation of therapy a more realistic option.

Azathioprine is often used as an alternative agent for longer-term immunosuppression. It is effective in 70% to 90% of patients with myasthenia gravis [2] and is often initiated in patients with an insufficient response to corticosteroids, as a steroid-sparing agent, or in patients in whom corticosteroids are contraindicated [3]. Azathioprine is limited by a relatively long delay before its effects are clinically evident, up to 6 to 12 months, but its side-effect spectrum compares favorably with steroids over a time frame of many years. If a patient tolerates a 50-mg per day test dose, the daily dose can be increased by 50 mg each week up to 2 to 3 mg per kg per day. The dose is reduced if the white blood cell count is less than 3,000 per mm^3; an elevated mean corpuscular volume can also be used to assess adequate response [4,29]. In up to 10% of patients, an influenza-like reaction characterized by fever, malaise, and myalgias occurs within the first few weeks of therapy and resolves after discontinuing the drug [2,29]. Patients should be screened for thiopurine methyltransferase (TPMT) deficiency; those homozygous for TPMT mutations cannot metabolize azathioprine and therefore should not receive the drug. Concurrent treatment with allopurinol should also be avoided as it interferes with the degradation of azathioprine, thereby increasing the risk of bone marrow and liver toxicity [29].

Cyclosporine appears to be as effective as azathioprine in the treatment of myasthenia gravis [30] and is used mainly in patients who are intolerant or refractory to azathioprine. Onset of clinical improvement is quicker than with azathioprine, with most patients noticing improvement after 1 to 3 months, and becoming maximal around 7 months [31]. Its major limitations are renal toxicity and hypertension, which are seen in about one-quarter of patients. To minimize side effects, the starting dose of 5 mg per kg per day can be given in two divided doses 12 hours apart, followed by adjustments to maintain a predose trough level in the range of 100 to 150 ng per L. Subsequent adjustments can be made depending on creatinine levels and clinical improvement, with the aim to reduce the dose as much as possible once maximal improvement is obtained [31]. Renal function (blood urea nitrogen and creatinine) must be continually monitored. Significant hypertension and preexisting renal disease are contraindications to the use of cyclosporine.

Another agent from the realm of transplant medicine, mycophenolate mofetil (CellCept), has also been used effectively for longer-term therapy. Several case series, retrospective analysis, and a small placebo controlled, double-blind trial suggested that mycophenolate mofetil is beneficial in patients with myasthenia gravis [32–34]. Because it is better tolerated than other immunosuppressants, it has become widely used. Recently, however, two large double-blinded randomized controlled trials failed to show any benefit of mycophenolate mofetil over placebo in patients with myasthenia gravis [35,36]. One study showed that mycophenolate mofetil was not superior to placebo during a steroid taper [35], while the other study showed no benefit in taking mycophenolate mofetil with 20 mg prednisone compared to taking prednisone alone [36]. Several factors have been proposed to explain these surprisingly negative results including the short duration of the trials, selection of generally mildly affected patients, and the unexpected significant response to low-dose prednisone [2]. Further studies are warranted to establish the role of mycophenolate mofetil in myasthenia. Despite this, mycophenolate mofetil is still widely used in the treatment of myasthenia gravis. The standard dose is 1,000 mg twice a day, but doses up to 3,000 mg per day may be used. Monthly complete blood counts should be performed to monitor for any evidence of myelosuppression.

In refractory cases in which it has proven difficult to achieve or maintain remission, high-dose cyclophosphamide has proven effective [2]. However, it has significant side effects including bone marrow toxicity, hemorrhagic cystitis, teratogenicity, and increased risk of infections and malignancies. Oral dosage ranges from 1 to 5 mg per kg per day [16]. Recently, Drachman and colleagues reported dramatic clinical improvement by "rebooting the immune system" in patients with refractory myasthenia using high-dose cyclophosphamide 50 mg per kg per day for 4 days, followed by granulocyte colony-stimulating factor; clinical improvement lasted several years in some patients [37].

Several case series have reported a beneficial response of rituximab in patients with refractory myasthenia gravis and in those with MuSK myasthenia gravis [38]. Patients tolerated the treatment without significant side effects, making this a promising drug for the future.

Cholinesterase Inhibitors

Cholinesterase inhibition was the mainstay of pharmacotherapy for myasthenia gravis before the advent of immunosuppressive therapies and thymectomy. Many patients are now maintained in remission on corticosteroids or other immunosuppressive agents, while others, in particular, those with mild nonprogressive or purely ocular disease, require only treatment with an oral anticholinesterase drug, such as pyridostigmine (Mestinon). If an acutely deteriorating patient has been taking a cholinesterase inhibitor, the possibility of cholinergic crisis should be entertained. Overdosage of cholinesterase inhibitors may produce weakness accompanied by muscarinic symptoms such as increased pulmonary and gastric secretions, bradycardia, nausea, vomiting, diarrhea, and nicotinic symptoms such as fasciculations [2,17]. Many authors advocate discontinuing anticholinesterase therapy during myasthenic crisis to minimize secretions, avoid potential exacerbation of weakness due to overdosage of cholinergic medications, and allow

easier assessment of response to other therapies [16,17]. It is reasonable to reinstitute anticholinesterase therapy when patients are stronger, starting at a low dosage and gradually increasing the dose until there is clear benefit [16].

The use of intravenous anticholinesterase therapy is controversial. Infusion of intravenous pyridostigmine at 1 to 2 mg per hour during crisis was found in one small retrospective study to be comparable to plasmapheresis [39]. However, intravenous therapy carries the risk of dangerous side effects such as cardiac arrhythmias, myocardial infarction (due to coronary vasospasm), airway obstruction, and increased pulmonary secretions [17,40]. It is therefore more prudent to hold cholinergic drugs until the patient is able to take them orally or through a nasogastric tube [17]. If intravenous anticholinesterase therapy is deemed necessary, neostigmine and pyridostigmine preparations are available in parenteral forms. One milligram of neostigmine given intravenously is roughly equivalent to 120 mg of pyridostigmine taken by mouth. Intravenous pyridostigmine is approximately 1/30th to 1/60th the dose of oral pyridostigmine.

PERIOPERATIVE MANAGEMENT OF THE MYASTHENIC PATIENT

An intercurrent problem requiring surgical intervention was a common source of major morbidity and mortality for myasthenics before the 1960s. Subsequent developments in critical care techniques, especially respiratory care, and in therapy of the underlying disease have dramatically improved this situation. Perioperative management must be compulsive, yet myasthenia gravis should rarely preclude surgical treatment that is otherwise indicated.

Preoperative Considerations

Myasthenia gravis is a major variable in surgical management, whether the surgery is elective or emergent. A neurologist (preferably the neurologist who has been managing the patient) should be considered an integral member of the operative team. If the procedure is elective, the patient's myasthenic status should be optimized before anesthesia and surgery. Pulmonary functions should be reviewed in detail; if respiratory or bulbar muscle function is compromised, therapy adjustments should be undertaken to improve the patient's status. All therapeutic options should be considered, with the possible exception of corticosteroids. If the patient is not receiving steroids, it is prudent to forego or delay this treatment until after surgery, because corticosteroids may increase the risk of infection and retard wound healing. If the patient is already receiving corticosteroids, therapy should be continued, with a short-term increment in dose to compensate for the added stress of anesthesia and surgery. Plasmapheresis or intravenous human immune globulin is often useful in the preoperative setting, providing a transient therapeutic benefit through the preoperative and postoperative periods. Once dose and regimen are optimized, cholinesterase inhibitors may be continued up to the time of surgery. They should then be discontinued because they stimulate respiratory secretions.

It is crucial that all physicians involved in perioperative management of the myasthenic are aware of the particular medications that may accentuate the underlying defect in neuromuscular transmission. It is appropriate to post a warning regarding specific medications on the patient's chart, in a manner analogous to that for medication allergies. Neuromuscular blockade should be avoided during surgery unless absolutely essential; if required, the shortest-acting agents should be used at minimal doses. Accentuated and prolonged effects should be anticipated. Aminoglycoside antibiotics should also be avoided when alternatives are available. There is no clear consensus in favor of any one halogenated anesthetic agent; ether adversely affects neuromuscular transmission. Again, close attention to metabolic homeostasis cannot be overemphasized.

Postoperative Care

Postoperative care of the myasthenic patient should not differ greatly from that of other patients, provided preoperative and intraoperative management has been successful. The patient's status before surgery is often the best indicator of the postoperative course. Intubation and mechanical ventilatory support must be continued until the patient is alert and responsive and demonstrates and maintains adequate pulmonary function. Serial pulmonary functions indicate when the patient can be extubated. An FVC greater than 20 mL per kg and MIP less than (i.e., more negative than) -40 cm H_2O are minimum requirements. If needed, cholinesterase inhibitors may be resumed as a continuous intravenous infusion until bowel function is restored and oral intake allowed. Increased sensitivity to cholinesterase inhibitors is the norm after surgical procedures, especially thymectomy. Resumption at a rate of no more than one-half the preoperative equivalent is often sufficient. Subsequent adjustments should reflect clinical indices. The myasthenic whose neuromuscular function deteriorates during the postoperative period is the exception. In all probability, an intercurrent reversible factor underlies the deterioration. The spectrum of metabolic, infectious, and pharmacologic issues discussed previously should be reviewed.

Thymectomy

After several decades of controversy, there is a consensus that thymectomy favorably alters the natural history of myasthenia gravis, especially in younger patients, independent of the presence or degree of thymic hyperplasia [41]. Thymectomy should be considered early in the course of myasthenia, except in elderly, frail patients. Thymectomy remains an elective procedure, however. The myasthenic with marginal respiratory or bulbar function should be optimally treated before surgery. The perioperative management considerations discussed earlier apply to prethymectomy and postthymectomy management. Some controversy persists regarding the appropriate thymectomy procedure. Most centers favor the transsternal approach. Although more invasive, this approach facilitates recognition and removal of all thymus tissue and avoids postoperative respiratory compromise. There are some proponents of transcervical mediastinoscopic thymectomy; in experienced hands, this remains an alternative. Thymectomy by conventional thoracotomy has no place in the treatment of myasthenia.

CONCLUSION

Respiratory failure is no longer the source of major morbidity and mortality in myasthenia gravis that it once was. When it does occur, appropriate ventilatory support and airway protection provide time for resolution of any intercurrent problems and therapy of the underlying myasthenia. Plasmapheresis and immunosuppression are usually successful; extended intensive care stays should be rare occurrences. Treatment of myasthenia gravis with steroids, immunosuppressive agents, and thymectomy usually enables these patients to lead essentially normal lives.

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CHAPTER 177 ■ MISCELLANEOUS NEUROLOGIC PROBLEMS IN THE INTENSIVE CARE UNIT

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A wide variety of neurologic problems may confront the physician in the intensive care unit (ICU), including several important disorders for which basic information is not readily available. These include

- Suicidal hanging, electrical shock, acute carbon monoxide poisoning, and decompression sickness, which present so blatantly that the diagnosis is rarely in question, yet the range of clinical manifestations and their management may be unanticipated.
- Cerebral fat embolism, which is often not initially suspected if other surgical or medical issues take precedence.
- Singultus (hiccups), which is an all too common secondary problem that may further weaken the severely ill patient.

- Compression neuropathies, which may complicate prolonged bed rest.

SUICIDAL HANGING

Hanging is the second most common means of committing suicide in the United States [1]. Introduced in fifth-century England, hanging proceeded to become the official form of execution. Early on, there was no exact procedure, and most hangings resulted in slow strangulation [2]. Changes in techniques, such that the victim dropped at least his height and the hangman's knot being placed in the submental location, produced a consistently fatal bilateral axis-pedicle fracture, resulting in complete herniation of the disc and severance of the ligaments between C2 and C3 [3]. This injury causes almost immediate death by destroying the cardiac and respiratory centers, lacerating the carotid artery, and injuring the pharynx [2,3].

Suicidal hangings are rarely so expert, and death usually results from strangulation due to interruption of cerebral blood flow [4]. A minimal amount of compression occludes the jugular veins, while an increased force occludes the carotid arteries [5,6]. A much larger force is necessary to arrest blood flow in the vertebral arteries [5]. Pressure on the jugular veins from the noose results in venous obstruction and stagnation of cerebral blood flow, causing hypoxia and loss of consciousness [3]. Cervical muscle tone then decreases, allowing airway obstruction and arterial compression, further worsening hypoxia [3]. In addition, external compression of the carotid bodies or vagal sheath can increase parasympathetic tone, whereas pressure on the pericarotid area stimulates sympathetic tone; either can result in cardiac arrest [4,5]. The altered autonomic tone may also cause a release of catecholamines, resulting in neurogenic pulmonary edema, as well as affect the respiratory smooth muscle tone, causing respiratory acidosis and a further insult to cerebral oxygenation [3].

If blood flow is quickly restored, full recovery can often be expected. If the blood flow is interrupted for more than a few minutes, however, hypoxia causes cell death and cytotoxic and vasogenic edema, with increased intracranial pressure. There is selective vulnerability of the cerebral cortex (particularly the pyramidal cell layer), the globus pallidus, thalamus, hippocampus, and the cerebellar Purkinje cells to anoxia and ischemia.

Diagnosis

Although the diagnosis is rarely in doubt, the patient may show a range of findings, varying from rope burns to coma. In the immediate posthanging period, the patient most commonly shows evidence of an altered level of consciousness, ranging from restlessness, delirium, or violence to lethargy, stupor, or coma. Seizures, and rarely status epilepticus, may occur [4,5]. Hyperthermia may be present because of hypoxic damage to the hypothalamus [6]. Injury to the neck blood vessels occurs in 40% of patients, resulting in carotid dissection, thrombus formation, and distal ischemic infarcts [7]. Venous occlusion may lead to venous congestion, venous ischemia, and hemorrhage [8]. Development of the acute respiratory distress syndrome may result from central nervous system (CNS) catecholamine release, causing constriction of the pulmonary venules [3]. In incomplete hanging, the patient may also show signs of laryngeal and pharyngeal edema, resulting in hoarseness, dysphagia, and stridor [3,8]. Although infrequent in suicidal hangings, fracture of the odontoid and injury to the spinal cord may occur.

Careful neurologic examination should be performed, with particular attention to alterations in the level of consciousness and evidence of spinal cord injury, such as paraparesis, quadriparesis, or urinary retention. There should be frequent monitoring of vital signs for evidence of autonomic instability and stridor. Initial laboratory evaluations should include radiographs of the cervical spine, arterial blood gas determination, electrocardiogram, and cardiac monitoring. CT angiogram should also be considered if suspicious for dissection of the carotid artery [9].

Neuroimaging of the brain may be quite variable, from a normal head computed tomography (CT) scan in many patients, to evidence of edema, hemorrhage, and ischemia. Due to decreased blood flow and the resultant hypoxia, edema may be seen in the white matter tracts [10]. Subcortical and subarachnoid hemorrhages may result from venous occlusion, while ischemic insults may result from venous or arterial occlusion, particularly in the areas of greatest vulnerability: the basal ganglia, cortex, thalamus, and hippocampus [11].

Treatment

The patient may appear dead but might still be resuscitable. Patients quickly lose consciousness with hanging attempts, but may still have cardiac and respiratory function or can quickly regain these with prompt cardiopulmonary resuscitation (CPR). The goals of treatment are to maintain an adequate level of cerebral oxygenation, to decrease the raised intracranial pressure, and to monitor and treat any cardiac arrhythmias or respiratory distress that may develop. In hangings, the mechanical trauma induced by strangulation can also cause hemorrhage and edema in the paratracheal and laryngeal areas and result in a delayed but significant airway obstruction at any time within the first 24 hours. Endotracheal intubation may be required if there is evidence of hypoxia due to acute respiratory distress syndrome, airway obstruction, or increased intracranial pressure [8].

Other concerns in victims of hangings include fractures and thrombi. A fracture of the odontoid requires immediate neurosurgical or orthopedic intervention to stabilize the cervical spine and protect the cord from injury. A carotid thrombus requires prompt vascular intervention to remove the clot and restore patency and blood flow. In addition, assessing the patient for other evidence of self-inflicted injuries and intoxications is also warranted, as is a complete psychiatric evaluation once the patient is able to cooperate.

Course

The prognosis for recovery is not immediately apparent with the first neurologic examination. Many patients have made a full recovery despite an initial Glasgow Coma Scale (GCS) score of 3 [4]. However, the fatality rate for suicidal hangings may range from 60% to 70% [12]. Indicators for a good recovery include a hanging time of less than 5 minutes, a heartbeat present at the scene or in the emergency room, CPR initiated at the scene, a GCS score greater than 3, and an incomplete circumferential ligature [4]. Predictors of a poorer prognosis include evidence of cardiopulmonary arrest, a spontaneous respiratory rate less than 4 per minute, need for intubation, and neurogenic pulmonary edema [5].

Other neurologic sequelae can become manifest either in the immediate posthanging period or after a relatively asymptomatic latent period. The individual may show evidence of a confusional state, a circumscribed retrograde amnesia, Korsakoff's syndrome, or even progressive dementia [8]. Transient hemiparesis, aphasia, abnormal movements, motor restlessness, and myoclonic jerks also can characterize this period [8]. Ear numbness may result from injury to the greater auricular nerve [13]. Three more severe outcomes have also been observed: (a) comatose state with minor neurologic improvement

and death; (b) early neurologic recovery, followed by cerebral edema with uncontrollable uncal herniation and severe morbidity or mortality; and (c) complete neurologic recovery, followed by delayed encephalopathy and death [3]. Most patients who survive recover to variable degrees.

ELECTRICAL INJURIES

Approximately 4,000 injuries and 1,000 deaths from electrical shock occur annually in the United States. Most fatalities occur in the workplace, but one third result from contact with household current [14]. Approximately 400 people per year are affected by lightning strikes, with one-third of victims dying due to their exposure [15].

Pathophysiology

Electrical and lightning injuries are exceedingly variable and dependent on a number of factors. Current flowing between two potentials, or amperage, is equal to the voltage divided by the resistance to current flow (I = V/R). Current is generated by either an electrical source or a lightning strike. Current may be direct (DC), as with lightning, or alternating (AC), as with most household appliances. Alternating current has a tendency to produce tetanic contractions that prevent voluntary release from the current source, thus prolonging the electrical contact time and increasing the potential for injury. Higher voltages, such as those that occur with lightning or with contact with high-voltage conductors, produce more severe injuries than those due to low voltages. Wet skin and tissues high in water content provide low resistance to current flow and are at a higher risk for injury, while tissues high in fat and air, such as hollow organs, provide high resistance. Nerves and blood vessels have lower than expected resistances, and thus are more sensitive to electrical injury than their water content would suggest [16]. Other variables that affect the severity of damage include the current pathway (i.e., whether it involves the heart, diaphragm, spinal cord, or brain), the area of current contact and exit, and the duration of contact [16].

In addition, lightning injuries are classified according to the type of exposure [17]. "Direct strikes" involve direct contact between the lightning bolt and the highest point of the victim, often the head. "Side flash" involves the spread of electricity from the lightning bolt to a nearby object and then to the patient. Side flash victims are typically exposed to less voltage and current than with a direct strike. Finally, "stride current" involves the spread of electricity from the lightning bolt to the ground and then through contact points in the patient. Stride current patients are more likely to experience spinal cord injuries, as the current crosses through the spinal cord from one limb to another.

Neurologic Complications of Electrical and Lightning Injuries

Neurologic sequelae of electrical injuries affect both the central and peripheral nervous systems, with both immediate and long-term difficulties.

Immediate Effects

Immediate neurologic effects of electrical injuries are noted throughout the neuraxis. Ten percent to 50% of patients experience a brief loss of consciousness, as well as headache, retrograde amnesia, and confusion [18]. Patients with electrical and lightning injuries to the head may also suffer subarachnoid or parenchymal hemorrhages, particularly in the basal ganglia and brainstem [19]. In patients who suffer cardiac or respiratory arrest, posthypoxic encephalopathy may develop in "watershed" areas of the cerebral cortex. Less commonly, patients may present with cerebral infarction or a temporary cerebellar syndrome [19].

Catecholamine release may result in autonomic dysfunction, as evidenced by transitory hypertension, tachycardia, diaphoresis, vasoconstriction of the extremities, and fixed and dilated pupils [20]. Thus, lightning strike victims should receive full resuscitative efforts despite pupillary changes, as these may not indicate brainstem dysfunction. Lightning strike victims may also suffer "keraunoparalysis," a self-limited paralysis more often involving the lower extremities, accompanied by a lack of peripheral pulses, pale and cold extremities, and variable paresthesias [19]. Keraunoparalysis is presumably due to localized vasospasm from catecholamine release.

Acute spinal cord injuries are also seen, particularly with stride current injuries. The spectrum of spinal cord injuries includes paralysis, spasticity, autonomic dysfunction, and, later, chronic pain and pressure ulcers [19]. Acute neuropathies are typically not seen with lightning strikes, but may be seen with electrical injuries in association with compartment syndromes, local burns, or vascular injury [21]. Both electrical and lightning strike victims are vulnerable to the subacute development of cataracts, while lightning strike patients are peculiarly susceptible to tympanic membrane rupture, vertigo, and hearing loss [22,23].

Delayed Effects

Delayed effects of electrical and lightning injuries may also span the neuraxis. Recognized neuropsychiatric effects include depression, posttraumatic stress disorder, fatigue, irritability, and memory and concentration difficulties [24]. Movement disorders have also been described, such as transient dystonias, torticollis, and parkinsonism [19]. Delayed ophthalmologic and otologic consequences include cataracts, conductive and sensorineural hearing loss, and vertigo [22,23]. Delayed autonomic dysfunction may manifest as reflex sympathetic dystrophy, presenting as a limb with burning pain, cutaneous vasoconstriction, swelling, and sweating [20]. Prolonged and permanent spinal cord abnormalities may become manifest in the delayed development of a myelopathy or a motor neuronopathy [14,25]. Peripheral neuropathies may result from compression due to scarring and fibrosis from the original injury or delayed ischemia due to vascular occlusion [26]. Peripheral neuropathies are more likely to occur in areas directly involved by the electrical current, but may also occur in limbs that were not seemingly in the current path [27].

Evaluation

Initial evaluation of the electrical- or lightning-injured patient involves assessment of the scene and evaluation of safety. Disconnect electrical sources before evaluating the patient. Contrary to conventional mythology, lightning-strike victims are not electrically charged and may be examined immediately.

Assessment of cardiopulmonary status is essential, as many victims suffer cardiopulmonary arrest and may recover well if CPR is initiated promptly. Cardiac arrhythmias and asystole commonly accompany these injuries, as does respiratory arrest due to passage of current through the brainstem respiratory centers. Stabilization of the spine is also essential, due to potential spinal cord injuries and fractures from falls.

Neurologic Examination

The neurologic examination should begin with assessment of the level of consciousness. Initially, many patients are

comatose, but this is often brief and followed by a period of confusion and amnesia, lasting hours to days [28]. Seizures are uncommon. The cranial nerve examination may reveal fixed and dilated pupils, blindness, papilledema, partial hearing loss, and tinnitus. Rupture of the tympanic membranes may also be present with lightning injuries to the head. Evaluation of the motor system for focal weakness and reflex changes may indicate cerebral injuries, myelopathy, or neuropathy. Cerebral lesions, due to hemorrhage or infarction, may result in contralateral hemiparesis. Spinal cord injuries are more common in the cervical region and produce paraparesis or quadriparesis. Peripheral nerve injuries in the immediate assessment are typically located in areas of extensive burns. Sensory loss is less frequent than motor deficits and is maximal in burned areas.

Laboratory Evaluation

Laboratory evaluations should be focused on the known complications of electrical and lightning injuries. Serial determinations of electrolytes, renal function, and hematocrit are essential for assessing adequate fluid replacement. Serum creatine kinase and urinary myoglobin are useful measures of muscle necrosis. Arterial blood gases may reveal a metabolic acidosis. Electrocardiogram (ECG) and cardiac monitoring are used in patients with cardiopulmonary arrest or with known current pathways through the thorax, as delayed cardiac arrhythmias may develop. Radiologic examinations of the long bones, spine, and skull are indicated when fractures or deep burns are suspected based on the history and physical examination. Magnetic resonance imaging (MRI) or myelography may be used to assess spinal cord damage if signs of myelopathy are present. Cranial imaging is indicated when there is prolonged alteration of consciousness and may reveal intracranial hemorrhages, cerebral edema, or the effect of diffuse cerebral hypoxia. The electroencephalogram (EEG) is also useful to rule out status epilepticus in patients with prolonged unconsciousness. The EEG background may remain slow even when the mental status has returned to baseline. Nerve conduction studies and electromyography may be useful in localizing and following axonal and demyelinating electrical injuries to the peripheral nerves and plexi, although they are not generally used in the acute evaluation.

Management

Evaluation and treatment of medical concerns are essential for good neurologic recovery. Efforts should focus on circulatory volume, hydration status, renal function, acidosis, and electrolyte balance. Because high-voltage electric shock victims usually have myoglobinuria secondary to burns and deep tissue injury, their fluid needs are similar to those of crush injuries. Central venous pressure monitoring is usually needed, and urine output should be maintained at greater than 50 mL per hour. Alkalinization of the urine and osmotic diuresis with mannitol also help to prevent myoglobin nephropathy.

Extensive burns due to direct current or clothing ignition are best treated in specialized burn units. At times, skin grafts are required. Debridement of necrotic muscle and fasciotomy are sometimes necessary to prevent secondary ischemia from a compartment syndrome. Amputation is required if there is significant necrosis. In these patients, arteriography may assist in identifying the level of viability. Tetanus prophylaxis and prevention of superinfection are also needed. Spine and long-bone fractures require stabilization.

Recurrent seizures are treated with phenytoin (18 to 20 mg per kg loading dose followed by 5 to 7 mg per kg per day). Other antiepileptics, such as levetiracetam, could also be considered. Because fluid restriction is contraindicated, patients with signs of increased intracranial pressure require osmotic diuresis with mannitol. Intracranial pressure monitoring may be useful in patients with cerebral edema. Specific treatment for electrical spinal cord injuries is not available, and early institution of physical therapy is recommended. In patients with cardiac arrest, the hypothermia protocol could be considered.

Prognosis

Prognosis is difficult to ascertain for electrical injuries to the nervous system. Patients with deficits at presentation frequently recover fully, whereas those with delayed onset of neurologic deficits may have syndromes that progress over months to years.

CARBON MONOXIDE POISONING

Carbon monoxide is a colorless, tasteless, odorless gas that may give no warning of its presence. It is normally present in the atmosphere in a concentration of less than 0.001%, but a concentration of 0.1% can be lethal [29]. Carbon monoxide is found in automobile exhaust, fires, water heaters, charcoal-burning grills, methylene chloride, volcanic gas, and cigarette smoke. It is also endogenously formed from the degradation of hemoglobin, resulting in baseline carboxyhemoglobin saturation between 1% and 3% [29]. Smoking can raise the endogenous level to 6% to 7% saturation [29]. Carbon monoxide poisoning may occur in the acute and chronic setting. For further information on the pathogenesis, diagnosis, and treatment of carbon monoxide poisoning, see Chapter 64.

Diagnosis

It is important to consider carbon monoxide poisoning in the differential diagnosis of any individual who presents with an altered state of consciousness or headache, particularly in the setting of a long car ride or other exposure to poorly ventilated and incompletely combusted fuel. Of note, the carboxyhemoglobin levels are not indicative of the severity of toxicity and depend on factors such as duration of exposure, comorbid conditions, and ambient carbon monoxide concentration [30]. With mild intoxication, symptoms may include a mild headache, dyspnea on exertion, and fatigability [29]. With increasing levels of toxicity, more severe symptoms may include impaired motor dexterity, blurry vision, irritability, weakness, nausea, vomiting, and confusion [29]. At its most severe, carbon monoxide exposure may cause tachycardia, cardiac irritability, seizures, respiratory insufficiency, coma, and death [29]. In addition, there can be evidence of rhabdomyolysis, flame-shaped superficial retinal hemorrhages, and, occasionally, a cherry-red discoloration best appreciated in the lips, mucous membranes, and skin [29,31].

Furthermore, carboxyhemoglobin levels do not correlate well with the development of delayed neurologic sequelae [32]. In mild carbon monoxide intoxication, in which there is no loss of consciousness and carboxyhemoglobin levels are less than 5% in nonsmokers or less than 10% in smokers, only headache and dizziness at or before presentation were found to correlate with an increased incidence of delayed sequelae, including asthenia, headache, or decreased memory [33].

A head CT scan may be normal early on or show signs of cerebral edema as inferred from narrowed ventricles and effacement of the cerebral sulci. The degree of CT abnormalities does not predict the clinical course [34]. MRI findings may reveal diffuse, confluent diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery, and T_2 (time for

63% of transverse relaxation) hyperintensities bilaterally in the periventricular white matter, centrum semiovale [35,36], basal ganglia, particularly involving the globus pallidus, and the hippocampus [37]. The electroencephalogram usually demonstrates diffuse slowing but is generally of little prognostic value.

Treatment

The criteria for hospital admission include coma, loss of consciousness, or neurologic deficit at any time; any clinical or electrocardiographic signs of cardiac compromise; metabolic acidosis; abnormal chest radiograph; oxygen tension less than 60 mm Hg; and carboxyhemoglobin level greater than 10% in individuals with pregnancy, greater than 15% in those with cardiac disease, or greater than 25% in all other patients [31].

All patients should be treated with 100% oxygen as soon as the diagnosis of carbon monoxide poisoning is even considered. It should be administered through a tight-fitting nonrebreathing mask or after endotracheal intubation in severely sensorium-compromised patients. The administration of 100% oxygen can shorten the half-life of carbon monoxide from 4 to 5 hours to approximately 1 hour [30]. Oxygen should be administered until the carboxyhemoglobin level normalizes [29]. (See Chapters 62 and 64 for a discussion of hyperbaric oxygen therapy.)

Administering 100% oxygen and possibly hyperbaric oxygen therapy are also useful in treating acute cerebral edema, as is mechanical hyperventilation and maintaining fluid and electrolyte homeostasis. Steroids have not been effective in cerebral postanoxic states and may increase the risk of oxygen toxicity seizures if hyperbaric oxygen therapy is being considered [31].

Course

The delayed appearance of neurologic sequelae found in many posthypoxic states occurs with particular frequency and severity after carbon monoxide poisoning. Up to 30% of patients may succumb to the initial exposure and 25% may develop a progressive encephalopathy resulting in a persistent vegetative state, with a 50% mortality rate [34]. Later sequelae may include seizures, cortical blindness, scotomas, Korsakoff's psychosis, irritability, hemiplegia, chorea, and peripheral neuropathy.

Between 10% and 30% of patients develop delayed neurologic sequelae, and there are no guidelines to indicate which patients are at greatest risk [31]. Although there seems to be a rough correlation between duration of initial unconsciousness and increasing age with the development of delayed neurologic sequelae, even patients with mild toxicity can progress to develop the tardive signs [30]. The post–carbon monoxide syndrome begins 7 to 30 days after the initial insult and is characterized by gait disturbances, incontinence, and memory impairment, as well as signs of parkinsonism, mutism, and frontal lobe disinhibition [29,30,38]. The development of isolated cognitive impairment has considerable variability in the literature. Some report memory dysfunction, impaired attention, and affective disorders in moderate to severe carbon monoxide exposure, while other studies suggest that mildly exposed individuals have no cognitive impairments compared to matched controls in neuropsychiatric testing [30,39,40].

On average, 75% of affected individuals largely recover within a year of the insult, although 20% of these individuals continue to show evidence of mild to moderate impairment of memory and extrapyramidal function [41]. Although the specific cause of the delayed syndrome is unknown, it does correlate temporally with the pathologic findings of cerebral white matter demyelination found in the chronic stages of the illness as opposed to the largely gray matter edema, ischemia, and hemorrhagic necrosis found in the acute stage [42]. There is no specific treatment for the delayed neuropsychiatric syndrome, although symptomatic treatment, including cognitive therapies and dopamine agonists, may be of benefit in the short term [41].

DECOMPRESSION SICKNESS

Decompression sickness ("the bends") occurs when gases dissolved in body fluids come out of solution, forming bubbles in tissues and venous blood. Situations in which decompression sickness arises include rapid ascent to the surface by tunnel workers or scuba divers, decompression or rapid ascent in an airplane, and high-altitude flying with inadequate cabin pressurization. In these situations, nitrogen and other inert gases that supersaturate the tissues under high pressure are released as bubbles under conditions of decreased pressure. As the bubbles coalesce, they may cause local tissue ischemia because of compression or venous obstruction. The microcirculation is further compromised by capillary endothelial edema; by activation of platelets, coagulation factors, and complement; and by hemoconcentration due to fluid extravasation [43,44]. Nitrogen, the largest component of inspired air, is lipophilic, and thus gas bubbles are more likely to form in the bone marrow, fat, and spinal cord. Additionally, gas bubbles may result in barotrauma to the pulmonary beds, releasing further air emboli into the venous circulation [43,44].

Symptoms of decompression sickness are variable. In most cases, the onset is within 6 hours of decompression, but may be seen later at 12 to 24 hours [43]. Fulminant cases present earlier. Any organ system can be affected, and symptoms range from a pruritic skin rash ("the creeps"), cough ("the chokes"), and joint pain to paraplegia, vertigo, altered level of consciousness, seizures, shock, and apnea.

Almost 80% of patients with decompression sickness have neurologic symptoms. The most frequent neurologic presentation is with paresthesias, which may be diffuse or focal, and result from gas bubble formation in the skin, joints, peripheral nerves, or spinal cord. Weakness, ranging from monoparesis to quadriplegia secondary to spinal cord involvement, may also occur. Cerebral symptoms are infrequent and range from headache and lethargy to vertigo, visual disturbances, paralysis, and unconsciousness [43,44]. Vertigo, hearing loss, tinnitus, nausea, and vomiting are relatively common complaints, resulting from rupture of the cochlear and semicircular canal membranes.

Air embolism is a more serious decompression illness, and its onset is usually within 5 minutes of decompression. It probably results from tearing of the lung parenchyma secondary to overinflation as the gases in the lungs expand during ascent [43]. The gas escapes into the pulmonary vein and may embolize into large vessels [43]. Venous gas bubbles are effectively filtered by the lungs, but arterial embolism may also result from gas passing through a patent foramen ovale. Based on their buoyancy, the emboli often produce neurologic symptoms by floating into and occluding cerebral arterioles. Unconsciousness and stupor are the most frequent symptoms. Death from cardiopulmonary arrest may also occur. In most patients, improvement in symptoms accompanies the redistribution of the gas emboli to the venous circulation [43].

Recompression is the definitive treatment for decompression diseases. The patient should be transported in a pressurized aircraft to the nearest decompression chamber with minimal delay. (See Chapter 61 for a more detailed discussion of the management and therapy for decompression syndrome.) The Divers Alert Network also maintains a 24-hour phone consultation

service to assist with diving accidents, reached at (919) 684-9111.

Remarkable recovery may occur after recompression. Delay in treatment can limit its effectiveness, but recompression should be attempted even up to 2 weeks after the onset of symptoms. Relapses requiring repeated hyperbaric treatment may occur [45]. Patients with long-term sequelae from decompression illnesses should not be re-exposed to conditions that allow their recurrence.

CEREBRAL FAT EMBOLISM SYNDROME

Fat embolism syndrome is characterized by diffuse pulmonary insufficiency with hypoxemia, neurologic dysfunction, and petechiae occurring 12 to 48 hours after trauma [46,47]. At least subclinically, fat embolism is present after all fractures involving the long bones. It is clinically recognized in 0.5% to 2% of patients with long bone fractures and in 5% to 10% of patients who have sustained multiple fractures [48,49]. There are also reports of fat embolism syndrome occurring in the setting of orthopedic procedures, such as hip arthroplasty, intramedullary rods, and leg lengthening procedures [48,50]. There is an increased risk associated with a patent foramen ovale [49].

Pathogenesis

The two main pathogenetic hypotheses of fat embolism syndrome are the mechanical and chemical theories. The mechanical theory posits that physical disruption of bone and blood vessels at the fracture site allows free fat globules to enter venous sinusoids and then to embolize to the lungs [46]. The chemical theory proposes that a trauma-induced catecholamine surge results in lipid mobilization from the fat stores or the coalescence of chylomicrons into fat globules [46,51]. The fat emboli in the circulation may then be broken down by lipases in the lungs or systemic circulation, generating free fatty acids [46,47,52]. The toxic fatty acids stimulate the release of inflammatory mediators, increasing permeability of capillaries, generating acute respiratory distress syndrome (ARDS) and cerebral vasogenic edema [46,47]. Furthermore, the inflammatory mediators may increase platelet adhesion and coagulation [52]. Fat emboli, in conjunction with increased platelet adhesion, may arrest blood flow, resulting in cerebral ischemia and hemorrhage [47,52].

Cerebral fat emboli and ischemia, rather than cerebral anoxia, produce the neurologic damage seen in this condition. The brain is edematous and shows a leptomeningeal inflammatory reaction and cortical surface petechiae. Microscopically, there are fat emboli and ball, ring, and perivascular hemorrhages. The fat emboli are more prevalent in the gray matter, but the hemorrhages are more common in the centrum semiovale, internal capsule, and cerebral and cerebellar white matter [53]. Electron microscopy reveals intravascular fat vacuoles, breakdown of endothelial walls, swollen neurons, and glia [53].

Diagnosis

Characteristically, there is a symptom-free interval of 12 to 48 hours between the inciting trauma and the onset of fat embolism syndrome [46]. Altered consciousness or development of neurological deficits after a lucid interval following trauma should alert the physician to the possibility of fat embolism. The syndrome may present as a spectrum of disability, from subclinical presentations with only a decreased arterial partial pressure of oxygen (PaO_2), decreased platelets or hemoglobin, to a fulminant presentation. Gurd's diagnostic criteria for fat embolism syndrome include one or more major criteria (respiratory insufficiency, neurologic dysfunction, or petechial rash), four or more minor criteria (fever, tachycardia, retinal changes, jaundice, or renal changes), and one or more laboratory criteria (fat macroglobulinemia, decreased hemoglobin or platelets, or increased erythrocyte sedimentation rate) [47]. An alternative diagnostic scheme was proposed by Schonfeld [47], assigning a numerical score to similar criteria with a score of 5 or more suggestive of the diagnosis.

Sudden onset of fever, tachycardia, and tachypnea often herald onset of the syndrome. Respiratory distress and hypoxemia with an oxygen tension less than 60 mm Hg is common and may be the initial or only laboratory abnormality. The chest radiograph may be unremarkable in one-half of the cases, but fine stippling or hazy infiltrates of both lung fields should be sought as they are consistent with fat embolism syndrome [51].

Petechiae are present in 50% to 60% of clinically recognized cases and are most often found on the lower palpebral conjunctivae, neck, anterior axillary folds, and anterior chest wall [47]. There is an associated thrombocytopenia, believed to be caused by the consumption of platelets with their aggregation around the embolic fat droplets, and a progressive anemia with hemoglobin levels commonly less than 9.5 g per 100 mL [51]. Retinal fat emboli and lipuria are each in evidence in more than 50% of patients [51]. The retinal emboli appear as small rosaries of microinfarcts surrounding the macula of both eyes, which over the course of the following 10 to 14 days evolve into yellowish, fatty plaques [51].

The CNS manifestations range from confusion to coma, and although they almost always accompany respiratory insufficiency, they can be the initial and sometimes only symptomatic manifestation of fat embolism syndrome [47]. Impaired consciousness is the earliest recognizable sign. The symptoms can begin with restlessness and confusion and may evolve gradually or abruptly to stupor and coma. Coma, especially if it develops abruptly, portends a poor prognosis [46]. Focal or generalized seizures can occur and may antedate the onset of coma [47]. Decerebrate rigidity is found in up to 15% of cases, and pyramidal signs of hyperreflexia and extensor plantar responses are found in 30% to 70%. Focal neurologic signs, such as aphasia and hemiparesis, are usually restricted to patients with more severe disturbances of consciousness [47].

Neuroimaging of cerebral fat embolism syndrome reveals diffuse vasogenic and cytotoxic edema, as well as areas of hemorrhage and infarct. The most common finding on head CT is evidence of diffuse brain edema, as shown by small ventricles and flattened sulci [54]. Brain MRI performed within 48 hours of a neurologic change may reveal signs of cerebral fat embolism syndrome even earlier than CT. The DWI sequence can exhibit a "starfield" appearance, with dot-like hyperintensities, both patchy and confluent, in border zone areas of territorial gray matter, deep white matter, and basal ganglia [54]. The DWI changes are suggestive of cytotoxic edema. Later, T_2 hyperintensities appear as small subcortical foci in gray and white matter, indicative of vasogenic edema; an increased number of T_2-weighted hyperintensities correlates with a decreased Glasgow Coma Scale [55]. These T_2-weighted hyperintensities disappear with resolution of the neurologic symptoms [56]. The later MRI appearance of brain atrophy and residual multiple infarcts may be present, particularly in patients with a poorer outcome.

Treatment

Rapid immobilization of fractures and their early definitive management decreases the likelihood of fat embolism syndrome [51]. Sequential clinical examinations, chest

radiographs, and arterial blood gas determinations in patients believed to be at high risk may help identify early on those needing more aggressive care. These patients should have early and expedient replacement of fluids and blood and administration of 40% oxygen by mask [51].

The support of respiration and maintenance of arterial oxygen levels greater than 70 mm Hg sometimes requires intubation and mechanical ventilation. Placement of a central venous pressure line is useful in monitoring the patient for shock. Steroids have been advocated as treatment to blunt the inflammatory response, to help preserve vascular integrity, and to minimize interstitial edema formation, but there are as yet no controlled trials demonstrating a consistent benefit. A brain CT or MRI is indicated to assess whether there are any direct cerebral traumatic injuries accounting for neurologic symptoms.

Prognosis

Mortality in fat embolism syndrome can reach 10% to 20%, but recent improvements in management have lessened this rate [57]. Twenty-five percent of patients experience permanent neurologic deficits [53]. A favorable prognosis is more likely with normal muscle tone, active deep tendon reflexes, and retention of appropriate pain response [47]. If patients survive the pulmonary insufficiency, neurologic dysfunction is typically reversible [47]. A worse prognosis is portended by coma, severe ARDS, pneumonia, or congestive heart failure [46].

SINGULTUS (HICCUPS)

Hiccups are usually a benign and self-limited condition. Prolonged hiccups can produce fatigue, sleeplessness, weight loss, depression, difficulty in ventilation, and, in postoperative patients, wound dehiscence [58–60]. In intubated patients, persistent hiccups may result in hyperventilation, leading to a respiratory alkalosis [58].

Pathophysiology

Hiccups result from a sudden reflex contraction of the diaphragm, causing forceful inspiration, which is arrested almost immediately by glottic closure, producing the characteristic sound. Afferent pathways include the vagus and phrenic nerves and thoracic sympathetic fibers (T_6 to T_{12}). The efferent pathway includes the phrenic nerve to the diaphragm, the vagus nerve to the larynx, and the spinal nerves to the accessory muscles of inspiration. Although central control of this reflex is not well defined, it probably involves lower brainstem and upper cervical spinal levels, including the respiratory center, phrenic nerve nuclei, medullary reticular formation, and hypothalamus [61].

Etiology

Hiccups may result from a multitude of causes, due to injury or irritation of the afferent or efferent pathways or disease within the central control mechanism. Hiccups most frequently result from irritation of the stomach wall or diaphragm, leading to impulses along the phrenic and vagus nerves. Abdominal disorders causing hiccups include gastric ulceration, gastric distention, gastroesophageal reflux, hiatus hernia, cholecystitis, peritonitis, subdiaphragmatic abscess, ileus, and bowel obstruction. Thoracic disorders that precipitate hiccups include esophagitis, pericarditis, myocardial infarction, pneumonia, and neoplasm. More proximally along the course of the nerves, neck masses, such as neoplasm and goiter, may also result in hiccups. Brainstem neoplasm or ischemia, multiple sclerosis, arteriovenous malformations, and meningoencephalitis are CNS causes. Perioperative causes include neck extension, intubation, visceral traction, and intraoperative manipulation of efferent or afferent nerves [58]. Metabolic disorders, such as uremia, electrolyte abnormalities, alcohol intoxication, diabetes mellitus, and general anesthesia, have also been implicated [58,61]. Medications, most frequently corticosteroids and benzodiazepines, may also induce hiccups [62,63]. Recently, hiccups have been reported in four patients with Parkinson's disease, and dopamine agonists appeared to play a causative role [64,65]. Some patients have idiopathic or psychogenic hiccups.

Evaluation

A history of gastrointestinal, cardiac, pulmonary, or CNS complaints or surgery may assist in determining the etiology of intractable hiccups. The physical examination should rule out inflammation or neoplasm in the thorax, abdomen, CNS, and neck. Chest and abdominal radiographs are obtained routinely, and fluoroscopic evaluation of the diaphragm is sometimes needed. Radiographic or endoscopic evaluation of the gastrointestinal tract is sometimes warranted. If the CNS is implicated, cranial CT or MRI may be useful. Electrocardiography is required. Other investigations include determinations of electrolytes, renal function, glucose, creatine kinase (if myocardial infarction is suspected), and a toxicology screen for alcohol and barbiturates. Lumbar puncture is required if there is a suspicion of CNS infection. Electromyography may be useful if surgical therapy for hiccups is contemplated. Careful review of medications for potential causative agents is indicated.

Management

Initial management includes identification and treatment of disorders that may cause hiccups, such as inflammation, infection, or gastric dilatation. When this is unsuccessful, nonpharmacologic and pharmacologic treatments are available for intractable hiccups.

Nonpharmacologic therapies alter the reflex arc responsible for hiccups. Pharyngeal stimulation may resolve hiccups, either by nasogastric intubation, swallowing dry granulated sugar, or by the introduction of a red rubber catheter through the mouth or nares, followed by a jerky to-and-fro movement [58]. Pharyngeal stimulation tends to be a temporary measure. Counterstimulation of the vagus nerve by pressure on eyeballs, rectal massage, or irritating the tympanic membrane may also alleviate hiccups [61]. Breathing into a paper bag, gasping with fright, Valsalva maneuver, and supramaximal inspiration possibly abolish hiccups by interrupting the stimulus for respiration or increasing the carbon dioxide concentration [66]. Case reports of acupuncture therapy also document effectiveness for refractory hiccups [59].

If nonpharmacologic therapies are ineffective, drug therapy should be initiated. Baclofen 5 mg orally three times a day, increased to 10 mg three times a day, has been effective in decreasing and potentially eliminating hiccups [61]. Alternatively, chlorpromazine taken 25 to 50 mg orally or intramuscularly three or four times a day has also been effective. If this is ineffective in 2 to 3 days, then a slow intravenous infusion of chlorpromazine 25 to 50 mg in 500 to 1,000 mL of normal saline is indicated. Although hypotension may result from intravenous (IV) administration, chlorpromazine may be most effective by this route [67]. If IV chlorpromazine is ineffective, it should be discontinued and 10 mg of metoclopramide given orally four times per day. Other medications used in refractory

patients include haloperidol (5 mg three times per day), anticonvulsants (e.g., gabapentin, phenytoin, carbamazepine, and valproic acid), amitriptyline, nifedipine, nimodipine, and amantadine [67].

Most patients respond to mechanical or drug therapy. In refractory cases, transcutaneous stimulation of the phrenic nerve, transesophageal diaphragmatic pacing, vagus nerve stimulation, phrenic nerve block or ablation, or microvascular decompression of the vagus nerve may be useful [60,67–70]. Because there are multiple efferent pathways involved, hiccups may remain even after phrenic nerve ablation.

COMPRESSION NEUROPATHIES

Compression neuropathies are common in the general population. In the ICU population, several nerves are particularly at risk, compression of which may result in delayed morbidity. The ulnar nerve may be compressed in the condylar groove posterior to the medial epicondyle when the arms are positioned in a flexed, pronated, or semipronated fashion, or when the flexed elbows are used by the patient for repositioning. Ulnar nerve palsy causes weakness of the intrinsic muscles of the hand and numbness of the fourth and fifth fingers. The peroneal nerve is also at risk where it courses around the fibular head. The everted immobile position of the leg in severely weak or paralyzed patients contributes to its vulnerability. Other compression neuropathies and brachial plexopathy may result from positions assumed during prolonged coma before hospitalization. Hematomas resulting from clotting disorders, anticoagulation, local injection, arterial puncture, or phlebotomy may also compress the peripheral nerves and plexi. Evaluation of compression neuropathies includes an EMG to localize the lesion. Proper positioning of the limbs to avoid compression of these nerves between the bed and bony prominences is key to prevention.

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CHAPTER 178 ■ SUBARACHNOID HEMORRHAGE

WILEY HALL, MAJAZ MOONIS AND JOHN P. WEAVER

Intracranial hemorrhage after rupture of saccular aneurysms accounts for 6% to 8% of all strokes affecting young adults. Intracranial aneurysms are found in approximately 5% of the population at autopsy and rupture at a rate of 4 to 10 per 100,000 population per year, with a 25% mortality during the first 24 hours [1]. Current mortality rates vary between 35% and 50%. Up to 30% die within the first 2 weeks, and 45% die within 30 days after the initial event. Fifty percent of the survivors are left with significant neurologic impairment [2–4]. As a rule, intensive care medical and surgical interventions are necessary in the management of these cases [5,6].

Subarachnoid hemorrhage (SAH) represents a potentially highly treatable form of stroke. Presently, the usual care of an aneurysmal SAH patient includes early aneurysm repair to limit rebleeding, a calcium channel antagonist to ameliorate cerebral injury secondary to vasospasm, intravascular volume maintenance to address any blood volume deficit, and some form of hemodynamic manipulation. Improvements in functional outcome are due to early intervention, supportive intensive care management, and modern methods of treatment, including cerebral protection, interventional neuroradiology, cerebrospinal fluid (CSF) manipulation, and hemodynamic management [5,6].

PATHOGENESIS

Saccular, or berry, aneurysms must be distinguished from other types of intracerebral aneurysms such as traumatic, dissecting, mycotic, and tumor-related aneurysms. Saccular aneurysms lack the normal muscular media and elastic lamina layers [7]. Eighty-five percent of saccular aneurysms are located in the anterior circulation; 15% are in the posterior circulation [8]. Common sites for aneurysms are at the junction of the anterior cerebral and anterior communicating arteries, the origin of the posterior communicating artery, the middle cerebral artery trifurcation, and at the top of the basilar artery. Less common are those located at the cavernous carotid, the internal carotid bifurcation, the distal anterior cerebral, and the proximal basilar arteries. Twelve percent to 31% of patients have multiple aneurysms. Nine percent to 19% have aneurysms located at identical sites bilaterally (mirror aneurysms), and multiple aneurysms may occur within families [9]. Systemic diseases such as polycystic kidney, Marfan's syndrome, Ehlers–Danlos syndrome, pseudoxanthoma elasticum, fibromuscular dysplasia, and coarctation of the aorta are associated with an increased incidence of intracerebral aneurysms [10,11].

It is unclear at present whether aneurysms have a congenital/hereditary origin or result from subsequent degenerative mechanisms. Supporting a congenital theory for aneurysm occurrence, individuals with a single primary relative with an intracranial aneurysm are at a 1.8 fold increased risk of intracranial aneurysm; those with two primary relatives have a 4.2 fold increased risk. Supporting the degenerative theory, there is an increased incidence of intracranial aneurysms in patients with hypertension, cigarette abuse, and alcohol abuse, and in the majority of cases, a family history of aneurysms is absent [11–14].

Risk of Rupture in Unruptured Intracranial Aneurysms

Ideally, the goal of treatment would be to prevent SAH, which carries a high mortality and morbidity. With increasing

use of magnetic resonance angiography (MRA) and high-resolution computed tomography angiography (CTA), incidental or asymptomatic small aneurysms are increasingly recognized before rupture. It is important to estimate the risk of aneurysmal rupture in these cases, which depends on critical size, location, or morphology of the aneurysm itself.

Data from a large, multicenter, prospective study—the International Study of Unruptured Intracranial Aneurysms [15]—suggests that the critical size associated with increased risk of rupture is 10 mm. Patients with unruptured intracranial aneurysms who have not had a prior SAH have a lower risk of aneurysmal rupture than with those in whom another aneurysm has previously ruptured. The annual risk of rupture of unruptured intracranial aneurysms smaller than 10 mm in patients with no previous SAH is 0.05% per year, compared with 0.5% per year in those with a prior SAH. In addition to size, aneurysm location was also predictive of subsequent rupture. Basilar tip aneurysms had the highest risk of rupture [15].

Data from the International Study of Unruptured Intracranial Aneurysms study conflicts with the experience at many centers that the majority of SAHs are attributable to aneurysms less than 10 mm. A smaller study [16] prospectively examining 118 consecutive patients with intracranial aneurysms found that, of 83 ruptured aneurysms, 81.9% and 59% were under 10 and 7 mm, respectively. Mean height and width were 6.7 and 6.1 mm. Seventy-two unruptured aneurysms were found to have similar size distributions, and mean height and width were 5.7 mm. The lack of conclusive evidence regarding prevalence of unruptured intracranial aneurysms in the general population and the absence of a screening tool that is sensitive, cost-effective, and safe enough makes optimal management of unruptured intracranial aneurysms a continuing challenge.

SYMPTOMS

The signs and symptoms of intracranial aneurysms result from their expansion or rupture. Aneurysmal expansion can lead to localized headache, facial pain, pupillary dilatation and ptosis from oculomotor nerve compression, and visual field defects from optic nerve or chiasm compression. Warning leak or "sentinel" hemorrhage occurs in approximately 20% of patients and is characterized by nuchal rigidity or meningismus that usually lasts at least 48 hours. The event is misdiagnosed in 20% to 40% as muscular-tension headache, migraine, sinusitis, viral syndrome, aseptic meningitis, or malingering [17]. Evidence of aneurysmal expansion or warning leak must be regarded with a high index of suspicion because such events precede major hemorrhage. Neurologic and functional outcomes are greatly improved if the patient is treated while neurologically intact before hemorrhage [18].

Aneurysmal rupture typically produces severe headache which is maximal at onset and is associated with neck pain, nausea, vomiting, photophobia, and lethargy. At the time of rupture, patients may lose consciousness and may demonstrate abducens nerve palsy, subhyaloid hemorrhages, or papilledema, reflecting the acute rise in intracranial pressure (ICP) that may transiently equal mean arterial pressure [19]. Other focal symptoms may also develop. Early seizures after SAH (8% to 11%) reflect a rise in ICP and are not indicative of the site or severity of rupture [20,21].

CLINICAL GRADING AND PROGNOSIS

The clinical grading scale developed by Hunt and Hess [22] is useful in estimating the patient's prognosis (Table 178.1). Grades I and II at presentation have a relatively good prognosis, whereas grades IV and V have a poor prognosis, and grade III an intermediate prognosis. The Glasgow Coma Scale is also useful in predicting outcome after early surgical intervention [23].

TABLE 178.1

HUNT AND HESS GRADING SCALE[a]

Grade	Symptoms
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate-to-severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate-to-severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund appearance

[a]Serious systemic diseases, such as hypertension, diabetes, severe arteriosclerosis, chronic obstructive pulmonary disease, and severe vasospasm, result in placement of the patient in the next less-favorable category.

DIAGNOSTIC EVALUATION

If SAH is suspected, an urgent noncontrast head CT should be obtained to identify, localize, and quantify the hemorrhage. CT imaging is 98% to 100% sensitive in the first 12 hours after SAH, declining to under 85% sensitive 6 days following a hemorrhage [6]. A lumbar puncture is indicated if the CT is nondiagnostic. CT scan may be negative in up to 35% of patients with sentinel leaks [24]. CT angiography (CTA) is the preferred study in the emergent surgical setting, and is often used when the presence of a large parenchymal clot makes delay for conventional arteriography unacceptable. CTA uses a contrast-enhanced high-speed spiral (helical) CT performed with reconstruction of the axially acquired data into angiographic images. CTA can demonstrate aneurysms of 2- to 3-mm size with sensitivities of 77% to 97% and specificities of 87% to 100% [25,26].

Traumatic lumbar puncture and SAH are distinguished by xanthochromia, demonstrated by spectrophotometric analysis of a centrifuged sample of the CSF [27]. Cell counts remain uniform in all tubes of CSF in a true SAH, and blood clots do not form. The CSF protein is usually elevated and glucose may be very slightly reduced. Opening pressure at the time of lumbar puncture may reflect the elevation of ICP.

Four-vessel cerebral angiography is necessary to localize the aneurysm, define the vascular anatomy, and assess vasospasm and the possible presence of multiple aneurysms. It should be performed within 24 hours after initial hemorrhage. If angiography does not reveal an aneurysm, magnetic resonance imaging and angiography can be performed to reveal aneurysms larger than 3 mm. If these studies are also negative, angiography is repeated in 1 to 3 weeks because acutely, intraluminal thrombus and vasospasm can interfere with angiographic visualization of aneurysms [6,28,29].

GENERAL MEDICAL MANAGEMENT

Complications of SAH are fatal in 25% of cases [15,27]. General preoperative medical management should include provisions for quiet bed rest, head elevation to improve cerebral

venous return, good pulmonary toilet to avoid atelectasis and pneumonia, and prophylaxis against thrombophlebitis with pneumatic boots. Patients should receive stool softeners. Nausea and vomiting can be controlled with antiemetics. Pain control is best accomplished with agents such as morphine or fentanyl. Mean arterial pressures higher than 100 mm Hg should be lowered gently until repair of the aneurysm can be achieved, but agents that can depress consciousness such as α-methyldopa should be avoided. Blood pressure is managed with beta-blocking agents; these agents may also reduce the risks of cardiac arrhythmias.

After SAH there may be a salt-wasting diuresis. Suggested mechanisms include an increase in circulating atrial natriuretic peptide. This syndrome is distinguished from the syndrome of inappropriate antidiuretic hormone by urine output and urine chemistry; both may result in hyponatremia. Accordingly, fluid input and output must be followed closely along with serum electrolytes and osmolality.

Seizures have been reported to occur in up to 18% of patients with SAH at onset, and are less common in hospitalized patients, recently reported at 4% [30]. The need for prophylactic anticonvulsants is controversial, and phenytoin remains the most common anticonvulsant used, though recent studies suggest a worse cognitive outcome with its use [31]. Levetiracetam is sometimes substituted if hepatic enzymes rise or suspected drug fever occurs, but data on its efficacy in this setting is as yet unavailable.

Elevation of ICP must be treated promptly with an agent such as mannitol. The use of dexamethasone for cerebral edema is restricted to patients with postoperative edema due to retractor manipulation, and is used to blunt headache caused by meningeal irritation; it has been reported anecdotally to shorten the course of hydrocephalus after SAH as well.

CARDIAC FUNCTION AFTER SUBARACHNOID HEMORRHAGE

Cardiac dysrhythmias may complicate care following SAH; a variety of mechanisms have been proposed. Increased levels of circulating catecholamines influence the α-receptors of the myocardium and can result in prolonged myofibril contraction, eventually causing myofibrillar degeneration and necrosis. An alternative theory of myocardial injury suggests that coronary artery spasm is the mechanism for the myocytolysis. SAH is the most frequent neurologic cause for electrocardiographic changes, which include large upright T waves and prolonged QT intervals (on average, approximately 0.53 seconds). In addition, prominent U waves, inverted T waves, and minor elevation or depression of the ST segment can occur. Despite ST-T changes, the incidence of myocardial ischemia remains low [32,33]. Pathologic Q waves are not common in SAH and suggest the need for further investigations for myocardial infarction. Patients with coronary artery vasospasm have a worse prognosis [34]. Arrhythmias are very common: a prospective study of 120 patients performed by using Holter monitoring indicated a 90% incidence of ventricular and supraventricular arrhythmias in the first 48 hours of hospitalization [35]. These do not appear to account for significant mortality.

NEUROLOGIC COMPLICATIONS

Aneurysmal rebleeding, hydrocephalus, and cerebral vasospasm with ischemia are the three major neurologic complications after SAH.

Rebleeding is a serious and frequent neurologic complication of SAH, carrying a mortality rate from 50% to 70% [5,6,9]. The peak incidence of rebleeding occurs during the first day after SAH, and a secondary peak occurs 1 week later. The rerupture risk for an untreated ruptured aneurysm is 23% at 2 weeks, 35% to 42% at 4 weeks, and 50% within 6 months [29]. Clinically, patients suffer with increasing headache, nausea, vomiting, depressed level of consciousness, and the appearance of new neurologic deficits. Occasionally, seizures occur, but they have not been shown to be a cause of rebleeding. Attempts to prevent rebleeding by drug-induced hypotension and bed rest have not been successful [36]. Antifibrinolytics decrease the rate of rebleeding, but older studies associate their use with increased incidence of ischemic insults from vasospasm [37,38]. Modern approaches including early aneurysm repair and intravascular therapy for vasospasm may ameliorate these issues, but antifibrinolytics are not strongly recommended [6].

Hydrocephalus can develop acutely within the first few hours after SAH because of impaired CSF resorption at the arachnoid granulations or intraventricular blood causing obstruction of CSF outflow. Clinically significant hydrocephalus developing subacutely over a few days or weeks after SAH is manifested by the loss of vertical gaze and progressive lethargy. Patients may appear to be abulic. Ventricular CSF drainage may be indicated if the clinical neurologic examination deteriorates or for any obtunded patient with hydrocephalus. CSF drainage is limited in patients with unprotected aneurysms because there is a danger of rerupture associated with abrupt decreases in ICP. A delayed form of hydrocephalus manifested by cognitive changes and gait disorders may be observed several weeks after the SAH; in these cases, a ventriculoperitoneal shunt may be indicated [5].

Stroke due to vasospasm is a major cause of morbidity and mortality in the postoperative period. Several controlled studies have shown an important role for the calcium antagonist nimodipine in ameliorating neurologic deficits caused by vasospasm. Beneficial effects are probably related to calcium channel–blocking properties, interfering with steps in the ischemic cascade [39–41]. The neurologic outcome and mortality rates of SAH patients prophylactically treated with nimodipine are improved 25% to 50% over control subjects. Fewer infarcts are noted in these patients, although there is no difference in the incidence or extent of arteriographic vasospasm [42–44]. The only adverse effect is mild transient hypotension. Current recommendations are to administer 60 mg of nimodipine orally every 4 hours for a 21-day course beginning at the onset of SAH.

ANEURYSM REPAIR

After acute angiography, patients should undergo aneurysm repair as soon as possible [44–46]. Many centers delay repair in patients who present overnight until the following day to allow approach by a well-rested team. Hemorrhages associated with large parenchymal clots are approached urgently. Delays of longer than 1 to 2 days are no longer common.

Aneurysms may be excluded from the systemic circulation by open surgical or endovascular approach. Open surgery offers definitive repair under direct visualization. The potential benefit of decreased hemorrhage burden in the subarachnoid space following irrigation has been suggested as a means to decrease vasospasm incidence, but this has not been well studied. Endovascular repair offers a less invasive approach, allowing obliteration of aneurysms which may be inaccessiuble to open surgery. Endovascular repair may also be of advantage in higher grade hemorrhages where cerebral edema complicates craniotomy, or in cases where late presentation or diagnosis increases the risk of open surgery. The choice of repair modality is best decided by a team approach combining experts from both interventional neuroradiology and vascular neurosurgery.

SURGICAL MANAGEMENT

Current surgical management necessitates craniotomy for clip occlusion of the aneurysmal neck, using mild systemic intraoperative hypotension, temporary proximal occlusion, and microsurgical techniques [47–49]. Unique problems that dictate the use of specialized techniques include vertebral-basilar system aneurysms, giant aneurysms (greater than 25 mm), and multiple aneurysms. Moreover, some giant aneurysms can be isolated from the intracerebral circulation with an antecedent arterial bypass from the superficial temporal artery, or saphenous vein graft from the cervical or petrous carotid artery. Internal carotid proximal occlusion may still be an effective way to reduce intra-aneurysmal pressure and reduce the occurrence of subsequent hemorrhage in certain aneurysms, but endovascular techniques have mostly replaced surgery to accomplish this treatment.

Postsurgical arteriograms are obtained by most neurosurgeons to assess successful clip placement or to diagnose vasospasm. The availability of portable digital angiography has made the possibility of intraoperative angiography quite practical. Barrow et al. [50] reported a series of 115 procedures with intraoperative arteriography in which 19 studies resulted in an altered surgical plan, presumably saving reoperation. Selection criteria currently rely on the operative difficulty of clip placement, visualization of clip placement, and surgical judgment.

HYPOTHERMIA AND INTRAOPERATIVE CEREBRAL PROTECTION

Hypothermia is a well-known cytoprotective strategy used in cardiac surgery. Animal investigation has demonstrated that a moderate decrease in brain temperature is associated with decreased concentrations of tissue neurotransmitters that might otherwise promote cascades of secondary neuronal and vascular injuries. In addition, the cerebral metabolic rate of oxygen uptake decreases as temperature falls; below 28°C cerebral electrical activity is minimal. While moderate hypothermia (31°C to 34°C) is commonly used as an adjunct to pharmacologic methods for neuroprotection during routine aneurysm surgeries [51,52], larger trials failed to detect an impact on outcome [53].

Deep hypothermia (22°C to 18°C) under barbiturate anesthesia with a short (10- to 15-minute) circulatory arrest is used rarely for reconstruction of giant aneurysms [54]. Previous bleeding disorders, predisposition to hemorrhage, and prior cardiopulmonary disease are all relative contraindications to deep hypothermia; this remains a high-morbidity procedure with fewer than 50% of patients achieving a good outcome. Reported complications include postoperative hemorrhage, deep vein thrombophlebitis, and pulmonary embolism.

INTERVENTIONAL NEURORADIOLOGY

The development of endovascular techniques has allowed increasingly safe and precise access to the cerebral vasculature. Endovascular balloon occlusion, coil technologies, angioplasty, and intraoperative arteriographic definition of vascular reconstruction represent technical advances that have improved outcomes. Endovascular therapy may be used to treat aneurysms by occlusion of the parent artery or by selective occlusion of the aneurysm.

The technique of endovascular balloon occlusion allows the fluoroscopically directed placement of a detachable silicone occlusive balloon within the aneurysmal sac [55]. In recent years, the devices have been abandoned for direct treatment of saccular aneurysms because of complications, including rupture, embolic events, and incomplete aneurysm obliteration. They are used, however, for the treatment of cavernous carotid fistula resulting from a ruptured aneurysm of the intracavernous carotid, and for parent artery occlusion. Temporary occlusion with neurologic monitoring of the patient's condition, electroencephalogram, cerebral blood flow (CBF), and transcranial Doppler (TCD) measurements are used before permanent proximal occlusion.

The most common endovascular approach to aneurysm occlusion is achieved by placing detachable platinum-alloy microcoils into the aneurysm sac. A low positive direct electric current transmitted through the guidewire detaches the coil from the stainless steel microcatheter by electrolysis and promotes intra-aneurysmal electrothrombosis by the attraction of local blood components. Clinical reports demonstrate a relatively high success rate for aneurysm obliteration and lower morbidity and mortality than balloon or free-coil embolization [56–58]. Advanced endovascular techniques, including stent-assisted coiling, balloon remodeling, and multicatheter techniques, allow aneurysms of various morphologies to be treated [59,60].

The International Subarachnoid Aneurysm Trial presented level I evidence supporting endovascular repair of ruptured aneurysms over surgical approach in most patients. The trial reported a 30.9% death or dependency rate in patients undergoing surgical repair, compared with 23.5% in those treated via endovascular approach. Higher rebleed rates at 1 and 4 years in the endovascular group did not offset the improvement in functional outcome [61,62]. The International Subarachnoid Aneurysm Trial was limited by a paucity of posterior circulation aneurysms, possibly because of evolving belief that these aneurysms are better approached via an endovascular approach and thus a perceived lack of clinical equipoise. Aneurysms with ratios of neck size to dome size greater than 0.5 and those with arterial branches arising from their domes or bases may be best treated surgically in most centers due to limitations in endovascular techniques.

POSTOPERATIVE MANAGEMENT

Care following repair of the ruptured aneurysm centers on limiting sequelae of SAH. Patients are monitored in the intensive care unit for evidence of vasospasm and hydrocephalus. Meticulous care to avoid pneumonia, deep venous thrombosis, and skin breakdown are mandatory. Nimodipine is continued for 21 days after hemorrhage [44]. Hypertensive, hypervolemic, hemodilution ("triple-H" or HHT) therapy has not been shown to prevent vasospasm, but is utilized when vasospasm is present to prevent infarction [44,63,64]. Maintenance of hematocrit above 30% is common, but evidence supporting its necessity in patients without evidence of coronary ischemia is lacking.

Cerebral vasospasm is a major cause of morbidity and mortality in patients recovering from SAH. Although noted angiographically in more than 70% of patients, it causes clinically evident symptoms due to cerebral ischemia in only 36% [65]. This difference probably reflects the adequacy of collateral circulation in the individual patient and the degree of vessel narrowing. Unlike rebleeding, the clinical presentation of vasospasm occurs progressively over a period of hours to days. It is rarely seen before the third day after hemorrhage, with a peak between days 4 to 12, and may rarely occur as long as 3 weeks after SAH [5,6]. The neurologic deficits are correlated with the areas of brain supplied by the narrowed arteries. Vasospasm is identified by angiography and noninvasively by TCD techniques.

TCD techniques are now widely used at most cerebrovascular centers. This simple bedside test is sensitive to the onset of cerebral vasospasm as arterial blood flow velocity increases with progressive vessel narrowing. Because the middle cerebral artery has little collateral circulation, diagnosis of vasospasm by TCD measurements is best validated in this vascular territory; TCD has an overall sensitivity of 68% to 94%, specificity of 86% to 100%, positive predictive value of 57% to 95%, and negative predictive value of 80% to 90% [66]. Fewer studies have documented sensitivity of TCD diagnosis for posterior circulation vasospasm [67]. This sensitivity is clinically useful because an elevated blood flow velocity is often detected before the occurrence of ischemic complications of vasospasm. More aggressive treatment aimed to increase cerebral perfusion pressure and improve circulation rheology can be instituted before the onset of neurologic impairment. Use of TCD for large groups of patients has allowed daily charting of the velocity changes that occur with the vasospasm syndrome. The time course of vasospasm onset and duration makes TCD a good tool to stratify patients into risk groups [68].

The amount of blood in the subarachnoid space and its location may predict the degree and location of delayed cerebral ischemic events. In theory, the pathogenesis of spasm is related to products of local erythrocyte breakdown that may be spasmogenic. Potential inducers of spasm include oxyhemoglobin, angiotensin, histamine, serotonin, prostaglandin, and catecholamines [4]. Vasospasm may occur because of endothelial structural changes caused by an inflammatory response, depression of vessel wall respiration, or damage from prolonged active arterial wall contraction. Other theories include impairment of normal vasodilatation, the mechanical effects of arterial compression by clot, and development of a proliferative vasculopathy. Pathologic specimens of affected vessels demonstrate intimal proliferation and medial necrosis. Thus, the pathogenesis of cerebral vasospasm is a complicated multifactorial process. Vasospasm occurs more frequently in patients with a poor clinical grade, thick focal blood clots, or a diffuse layer of blood in the subarachnoid space.

Modern multimodality monitoring of brain tissue oxygen tension and microdialysis of the interstitial space offers the promise of early diagnosis of vasospasm. Early case series suggest that brain tissue chemistry may change up to several days before the onset of vasospasm, best detected by detection of alterations in tissue lactate, lactate/pyruvate ratio, glutamate and other proteins using bedside microdialysis [69–71].

HYPERDYNAMIC THERAPY

Circulatory manipulation is a routine treatment for regional ischemia with predictable benefit [65,72]. Selection criteria for treatment include increasing blood flow velocity signals by TCD measurement, focal deficit, and global impairment of consciousness without hydrocephalus. While there is no proven preventative treatment for cerebral vasospasm, the current mainstay of therapy is hypervolemic hypertensive therapy or HHT. The aim is to augment cerebral perfusion and rheology by raising systolic blood pressure, cardiac output, and intravascular volume. Progress in this area has been predominantly in the area of small cohort studies of intermediate variables, CBF, and systemic blood volume [73–75]. A number of authors have demonstrated that elevation of systemic arterial pressure produces a significant increase in the regional CBF [76–78]. Typically, 20 to 30 mm Hg elevation of the mean arterial pressure increases CBF by 15 to 25 mL per minute per 100 g. In contrast, recent studies have failed to demonstrate a beneficial effect of hemodilution therapy on oxygen delivery in patients with vasospasm [79]. Vasopressors are used to keep systolic blood pressures 20 to 40 points higher than pretreatment levels, and plasma volume is maintained with normal saline and occasionally with albumin, hetastarch, or Plasmanate. This therapy is continued for 48 to 72 hours or until serial imaging studies improve before it is gradually withdrawn under close observation. Risks of therapy include myocardial infarction, congestive heart failure, dysrhythmias, and hemorrhagic infarcts. This treatment can be used most aggressively in the postoperative period because of the risks of aneurysmal rerupture before surgery. Early surgery and careful cardiac monitoring for congestive heart failure are necessary for the prevention of significant complications.

Angioplasty is another proven technique for treatment of cerebral vasospasm [80–82]. Higashida et al. [81] developed a soft silicone balloon that is navigated into the basilar, posterior cerebral (P1), middle cerebral (M1, M2), and anterior cerebral (A1, A2) arteries and provides appropriate pressures to dilate these vessels. Patient selection criteria for treatment include the presence of arteriographic vasospasm without infarction in a patient with a repaired aneurysm. A correlation of symptoms with the anatomy of the vascular narrowing is helpful but not always present because altered mental status is often the presenting symptom of vasospasm. Failure of calcium antagonist prophylaxis or complications of hypertensive hypervolemic therapy are appropriate indications for considering this procedure. Most successful angioplasties are performed in the first 48 hours after onset of major symptoms because the procedure is much less effective as a "salvage" technique after cerebrovascular reserve is depleted and vascular fibrosis occurs. Observations in a rabbit SAH model demonstrated that the initial vessel narrowing is related to vasospasm with subsequent anatomical fibrosis during the next 5 to 7 days, when it accounts for more than 60% of the caliber changes [83]. This identified the timing and extent of alteration of vessel inelastic elements in the production of vasospasm. Thus, angioplasty should be most effective early on before maximal fibrosis occurs. Angioplasty has also been used to treat catheter-induced spasm. Several groups have reported SAH patients who benefited from intra-arterial infusions of papaverine, verapamil, and nicardipine [84–86].

THROMBOLYSIS OF THE SUBARACHNOID SPACE

The degradation of hemoglobin in the cranial subarachnoid space produces a histologic and arteriographic picture consistent with vasospasm, and the severity of spasm/ischemia appears to relate to the amount of blood in the CSF space. Thus, there has been a longstanding interest in removing this spasmogen. A reduced incidence of vasospasm after intrathecal treatment with recombinant tissue-type plasminogen activator within the first 24 hours of onset of SAH, and a drop in the resistance to CSF outflow has been noted after experimental treatment with tissue plasminogen activator [87,88]. The use of intrathecal tissue plasminogen activator has been reported in 109 patients, with one hemorrhagic death due to an epidural hematoma, four nonfatal cases of epidural and intracerebral hematoma, and one extradural hematoma [89]. Arteriographic follow-up demonstrated a decreased incidence of arteriographic vasospasm.

FREE RADICAL SCAVENGERS IN SUBARACHNOID HEMORRHAGE

Free iron from the blood can lead to lipid peroxidation and free radical generation. Free radical scavengers may be useful in preventing further damage [90]. A controlled study in 208 patients using a free radical scavenging agent, nizofenone, demonstrated improvement based on functional recovery,

especially in patients with delayed ischemic symptoms, moderate severity of preoperative deficits (Hunt and Hess grades II or III), and diffuse high-density areas in pre- and postoperative CTs [91]. The nonglucocorticoid 21-aminosteroid tirilazad mesylate has been shown to inhibit lipid peroxidation and protect cell membranes by scavenging destructive-free radicals, but positive results of a European trial were not reproduced in a large multicenter North American trial [92–94]. In a post hoc subgroup analysis of the highest dose group, however, mortality was improved from 33% in the vehicle group to 5% in the patient subgroup that included men with admission grades IV and V.

RECOMMENDATIONS

The current literature for unruptured aneurysms has level IV and level V evidence and can support grade C recommendations. Patient factors, biases, and personal preferences influence treatment decisions and should be taken in consideration. Recommendations for ruptured aneurysms are more definite.

1. Management of unruptured intracranial aneurysms.
   a. In general, small incidental aneurysms less than 10 mm require follow-up rather than surgical intervention. Younger patients may require more aggressive management. Small aneurysms in this group may also be treated if there is rapid enlargement, daughter sac formation, or there is a history of familial intracranial aneurysms.
   b. Irrespective of size, coexisting or remaining aneurysms in patients with a previous history of SAH warrant consideration for aneurysm repair.
   c. Patients with basilar tip aneurysms 7 mm or more in diameter have a higher incidence of rupture and treatment should be considered.
   d. Decisions on approach to repair should be made by a team including a vascular neurosurgeon and an interventional neuroradiologist.
2. Management of ruptured aneurysms.

2.1 Aneurysms preferentially treated with surgical clipping include the following:
   a. Patients with poor vascular anatomy for endovascular approach
   b. Acutely ruptured aneurysms with symptomatic intracranial hematoma
   c. Recurrent aneurysms after coil embolization

2.2 Aneurysm preferentially treated by endovascular embolization with detachable coils
   a. Medically unstable patients
   b. Patients with poor neurologic condition (e.g., grade 4 or 5, established vasospasm, or severe brain swelling)
   c. Aneurysms with significant calcification
   d. Residual aneurysms after unsuccessful surgery

2.3 Patients should be monitored for vasospasm postoperatively using clinical examination and TCD if available.
   a. Hyperdynamic therapy is therapeutic but not preventive for vasospasm.
   b. Endovascular therapies for vasospasm should be employed when medical therapies fail.
   c. The calcium channel antagonist nimodipine should be given for the first 21 days following SAH.

3. Giant aneurysms greater than 2.5 cm should be approached on an individual basis. Location, accessibility, and collateral circulation all influence the decision to treat surgically or with endovascular management [15,95,96]. Patients are best approached on an individual basis with direct collaboration between neurosurgeon and interventionalist prior to repair.

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CHAPTER 179 ■ MENTAL STATUS DYSFUNCTION IN THE INTENSIVE CARE UNIT: POSTOPERATIVE COGNITIVE IMPAIRMENT

JOAN M. SWEARER AND SHASHIDHARA NANJUNDASWAMY

Cognitive dysfunction following major surgery is one of the common reasons neurologists are asked to evaluate postoperative patients in the intensive care unit (ICU): patients whose memory and intellectual abilities seem impaired when they otherwise appear to have recovered from the immediate effects of surgery. It is a major concern for the family, patient, and physician when a patient is found not to be intellectually the same on awakening following surgery as he or she was before.

There has been extensive research on cognitive dysfunction following major cardiac surgery and a growing literature from noncardiac surgery. In a literature review of cognitive decline following cardiac surgery published between 1985 and 2005, Newman et al. [1] reported that the incidence of decline noted within the first perioperative week varied from 50% to 70%. The incidence fell to 30% to 50% after 6 weeks, and to 20% to 40% at 6 months and 1 year. Differences in methods between studies (e.g., patient sampling, specific tests used, testing intervals, definitions of cognitive decline) make it difficult to compare the studies in literature reviews and meta-analyses directly. Despite these differences, increased age has been the most consistent factor associated with cognitive dysfunction; prolonged cardiopulmonary bypass has also been noted as a risk factor [1,2].

In a study of major noncardiac surgery [3], 1,064 patients aged 18 years and older completed neuropsychological testing before surgery, at hospital discharge, and 3 months after surgery. At 1 year postsurgery patients were contacted to determine survival status. At hospital discharge 36.6% of the young (18 to 39 years), 30.4% of the middle aged (40 to 59 years), and 41.4% of the elderly (60 years and older) had evidence of postoperative cognitive decline. At 3 months cognitive dysfunction was present in 5.7% young, 5.6% middle aged, and 12.7% elderly patients. Increased age, lower educational level, history of premorbid cerebral vascular accident (with no residual impairment), and cognitive decline at discharge were found to be independent risk factors for postoperative dysfunction at 3 months. Patients with postoperative cognitive decline were at increased risk of death in the first year postsurgery.

Although it is clear from these and other studies that postoperative cognitive decline can occur in elderly patients undergoing both major cardiac and noncardiac surgery, the precise pathophysiologic mechanisms have yet to be elucidated.

MENTAL STATUS EXAMINATION IN THE INTENSIVE CARE UNIT

The primary objectives of a mental status evaluation in the ICU are to screen for the presence of postoperative cognitive decline, to analyze both the nature and extent of the impairment, and to evaluate improvement or worsening over time. Cognitive changes may be obvious when there are gross deficits in learning, memory, attention, or concentration. The decline can also be subtle, with problems in initiative and planning ("executive" functions).

Many mental status screening tests are available [4–7], but none have been specifically developed for, or standardized in, the ICU. A brief screening test may provide a general impression of the patient's mental status, but the clinician must be able to assess areas of relative strength and weakness in greater depth. The following is offered as an outline for a mental status evaluation in the ICU [8–10].

Behavioral Observation and Patient Variables

Determination of the patient's level of wakefulness and arousal is the essential first step in a mental status examination: levels may range from deep coma to stupor, obtundation, normal alertness, hyperalertness, and manic states. Any further interpretation of mental status test results depends on full alertness, and is severely limited if arousal is not normal.

Test performance is also substantially influenced by the patient's ability to sustain attention. A patient who is easily distractible will perform poorly on most cognitive tests. Lack of motivation and effort during testing can have deleterious effects on test performance, and may lead to an overestimation of cognitive impairment. Abnormalities in mood and affect, and behavioral disturbances such as psychosis, disinhibition,

hyperactivity, or impulsivity will also negatively impact the patient's test performance.

Other patient variables that can influence test performance include demographic variables (e.g., premorbid cognitive abilities, age, gender, education, cultural background) and medical and psychosocial history (e.g., psychiatric history, social history, present life circumstances). A history from family members is extremely useful in assessing the patient's premorbid abilities.

Finally, test performance is compromised by postoperative pain, use of analgesic and sedating medications, limitations in arm/hand mobility, and possible sensory loss (e.g., hemianopia) or motor impairment (e.g., hemiparesis). Assessment of mental status becomes challenging, and the results uncertain, if the patient is on a ventilator.

Attention

The patient's span of attention can be assessed at the bedside using digit span, which also depends on immediate verbal recall. Repetition of digits both forward and backward should be evaluated. Both tests consist of increasingly longer strings of random number sequences that are presented aloud to the patient. The average score obtained by adults is seven digits forward and five digits backward.

Perseverance or the ability to sustain behavioral output can be measured at the bedside by mental tracking tests. Reciting the alphabet and counting from 1 to 40 by 3s are relatively easy mental tracking tests. Examples of more discriminating tracking tests include serial subtraction of 3s from 100 to 70 and reciting the months of the year backward.

Resistance to interference and response inhibition can be tested with motor sequencing tasks. Examples include the "go-no-go" test (when the examiner taps once, the patient taps twice, but when the examiner taps twice the patient does not tap [11]); and alternating sequences (e.g., copying a sequence of script such as "m n m n m n" [12]). Patients with impaired attention may perseverate on one element of the task rather than alternate between the sequences.

Speech and Language Functions

Speech output should be assessed for fluency (rate and effort of speech), articulation (normal or dysarthric), phrase length, prosody (melody, rhythm, inflection), content (semantics and syntax), and paraphasias (substitutions of rhyming alteration of words). Output can be observed in verbal responses to open-ended questions or by having the patient verbally describe a complex visual scene, such as a photograph ("propositional speech"). Disorders of repetition can be elicited by having the patient repeat phrases that vary in grammatical complexity (e.g., "no ifs, ands, or buts").

Auditory comprehension can be assessed at the bedside in a number of ways. Examples include pointing to named objects, such as body-part identification (e.g., "Point to your left thumb") and following multistage oral commands. Speech comprehension can also be assessed by asking "yes/no" questions such as "Do cows fly?"

Common objects (e.g., watch, pen, eyeglasses) can be used to test naming to confrontation. Component parts (e.g., lens, frame) may detect more subtle naming deficits. Oral reading and comprehension can be tested by having the patient read a brief passage from a newspaper, and then asked "yes-no" questions about its content.

Spontaneous writing and writing to dictation are excellent screening tests for aphasic writing deficits. Comprehension can also be assessed by having the patient follow written directions (e.g., "Point to the ceiling"). Word-list generation by specific category (e.g., animals, items found in supermarket or hardware store) and by specific initial letter is sensitive to both language and attentional sequencing disorders.

Memory Functions

Memory functions include immediate memory span, learning capacity and retention, and retrieval of previously learned information (recent and remote). Immediate memory span is commonly assessed with a digit span forward test (described previously). The ability to learn new information can be investigated in a number of ways. For example, three or four unrelated words are presented and the patient is instructed to remember them. After 5 minutes of other testing, the patient is asked to recall the words. Nonverbal learning can be assessed in a similar fashion using line drawings of simple geometric figures or by pointing to three or four objects in the room and asking the patient to recall them a few minutes later.

Remote memory can be tested by asking questions about political figures (e.g., naming the three previous presidents), dates of major world events (e.g., years of World War II), and personal history (e.g., name of high school attended).

Visuospatial and Visuoconstructive Abilities

Visuoconstructive ability is tested by having the patient copy simple figures (e.g., cube, daisy, interlocking pentagons). Spatial planning can be assessed with clock drawing. The patient is asked to draw the face of a clock and to fill in all the numbers. Left-sided visual inattention or hemispatial neglect is suggested if the patient places all the numerals on one side of the clock, or omits all numerals normally on one side. Capacity to process number/time relationships can be tested by having the patient "set the time to 10 minutes past 11 o'clock."

Executive Functions and Other Cognitive Abilities

Interpretation of proverbs (e.g., "the early bird catches the worm") evaluates concept formation or capacity for abstract thought. Ability to generate abstract thought can be assessed also by asking how word pairs are alike. An example of an easy similarity test pair is "broccoli–cauliflower"; a more difficult pair is "fish–dandelion." Mental arithmetic problems (e.g., "How many quarters are in $1.50?") test reasoning ability as well as immediate memory and concentration. Unfortunately, there are no reliable tests of judgment. Patients may be able to describe an appropriate response to how they would handle a small emergency, but may not behave so in a real emergency.

MENTAL STATUS DYSFUNCTION IN THE INTENSIVE CARE UNIT

Acute Confusional State (Delirium)

Delirium is a very common cause of mental dysfunction in postoperative patients in the ICU. The hallmark features of delirium are inattentiveness, confusion, and psychomotor agitation, although hypoactive delirium is also recognized. An alteration in sleep–wake pattern is evident. Fever, sepsis, metabolic and endocrine disturbances, as well as medication use or withdrawal,

or alcohol withdrawal, are among the causes of delirium; this is discussed in more detail in Chapter 197.

Focal Syndromes

Stroke is another adverse neurologic outcome from surgery—especially cardiac surgery [13] or endovascular procedures, such as angioplasty—and is usually recognized by the presence of focal or lateralizing deficits of sudden onset (see Chapter 173). Focal cognitive deficits include aphasia, apraxia, and agnosia; focal motor weakness and/or sensory loss may not be evident if the stroke involves more of the temporal–parietal areas due to low perfusion-border zone ischemia. Wernicke's type of receptive aphasia presents with a speech disturbance when the ischemic zone involves the posterior temporal lobe. In this condition, the patient speaks fluently but unintelligibly, is unable to comprehend speech, and can become agitated.

Postoperative Cognitive Decline/Dysfunction

As previously noted, changes in memory and concentration are often seen in the ICU in the initial postoperative period. These changes can, however, persist well beyond the immediate postoperative period when the effects of anesthesia and analgesia directly affecting cognitive functions have clearly worn off. Most mental status changes improve, but may continue following discharge, even weeks, months, and years later, with associated impaired quality of life and mortality [14,15].

Elderly patients undergoing major cardiac (e.g., coronary artery bypass grafting, thoracic vascular surgery) and major noncardiac (e.g., orthopedic, abdominal) surgery are at the greatest risk for postoperative cognitive decline. Other individual features that increase the risk of mental status dysfunction include previous cerebrovascular disease, previous and undetected cognitive impairment or dementia, and cardiovascular risk factors such as hypertension, diabetes, and peripheral vascular disease [1,2,16–18].

Intraoperative risk factors include surgical technique (e.g., duration of cardiopulmonary bypass, duration of aortic cross-clamping), hypotension, manipulation of diseased aorta, and the effects of general anesthesia and hypothermia. To assess these factors requires close scrutiny of the operative record, and of the anesthesia chart. Atherothromboembolic phenomena (microemboli) and hypoxia with watershed area injury secondary to hypoperfusion are possible causative mechanisms of postoperative cognitive dysfunction due to intraoperative events during surgery [1].

A number of postoperative factors can also affect cognitive status in the ICU, including the use of analgesics, degree of physical discomfort, and depression [16]. These factors may produce short-term but self-limited cognitive change. Nevertheless, they should be taken into account when assessing the mental status of a patient in the ICU.

SUMMARY

Testing for mental status dysfunction of a patient in the ICU can be a complex and difficult task. Interpretation of test results can be confounded by premorbid patient characteristics (e.g., presence of a dementing illness presurgically) and the patient's current status (e.g., drowsiness in the context of high-dose analgesics, sedatives, and other medications). Mental status testing should not be attempted if arousal is abnormal or if the patient is too ill. The approach to testing should be flexible and targeted to the individual patient's complaints and level of functioning. Postoperative cognitive changes range from obvious deficits in concentration and memory to subtle deficits in executive functions. Evidence of abnormality during a screening evaluation warrants a thorough neurologic evaluation.

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CHAPTER 180 ■ NEWLY ACQUIRED WEAKNESS IN THE INTENSIVE CARE UNIT: CRITICAL ILLNESS MYOPATHY AND NEUROPATHY

DAVID A. CHAD

Although preexisting neuromuscular disorders (such as myasthenia gravis and the Guillain–Barré syndrome) may cause severe weakness leading to an intensive care unit (ICU) admission, two of the most common causes of *newly acquired weakness arising in the ICU setting* are critical illness myopathy and critical illness polyneuropathy [1,2]. Critical illness myopathy is probably the major contributor to severe ICU-acquired weakness, causing most instances of failure to wean from a respirator in patients with severe systemic diseases in the ICU, while critical illness polyneuropathy affects 70% to 80% of patients with severe sepsis and multiorgan failure [3]. Even experienced clinicians have great difficulty distinguishing between the myopathy and the polyneuropathy of intensive care, especially because the two conditions often coexist in an individual patient [4–6]. In the sections that follow, we discuss each disorder and comment on the differential diagnosis of severe weakness arising in the ICU setting.

CRITICAL ILLNESS MYOPATHY

Diagnosis

The hallmark of critical illness myopathy is weakness that is typically diffuse in distribution, affecting both limb and neck muscles [7]. As is typical of most myopathic disorders, weakness tends to have a proximal predominance in the limbs, but it may also involve distal muscles profoundly. Tendon reflexes tend to be depressed but present, and on occasion, may be absent, possibly due to a generalized reduction in membrane excitability that occurs in sepsis [8]. There may be facial muscle involvement, and rarely, extraocular muscles are affected [9]; other muscles supplied by cranial nerves are usually spared. A serious and common complication of the myopathy is failure to wean from a ventilator due to marked weakness of the diaphragm. Although the majority of affected patients are adults, severe myopathic muscle weakness may occur in children who receive organ transplants [10].

Risk Factors

Critical illness myopathy develops in up to one-third of patients treated for status asthmaticus in the ICU; and in this population, intravenous corticosteroids and neuromuscular blocking agents are considered major risk factors [11]. Occasionally, the myopathy develops in patients who have received high-dose corticosteroids alone, without neuromuscular blocking agents, or in patients who have received neither corticosteroids nor neuromuscular blocking agents, but the latter group typically has severe systemic illness with multiorgan failure and sepsis [8]. Overall, critical illness myopathy accounts for 42% of weakness among patients in the surgical and medical ICU setting [12].

Laboratory Studies

Serum creatine kinase (CK), electromyography (EMG), and muscle biopsy are the most important and revealing studies in the diagnosis of ICU-acquired muscle weakness. An elevated CK level helps to support the diagnosis of a myopathic cause of weakness in an ICU patient, but in the myopathy of intensive care, the CK rise, which is found in about 50% of affected patients, only occurs early in the course of the illness, peaks within a few days of onset, and then declines back into the normal range [7].

EMG Studies

With nerve conduction studies, motor responses are typically low-amplitude or absent, while sensory responses are relatively preserved, with amplitudes that are > 80% of normal in two or more nerves (sensory responses may be reduced, however, when ICU polyneuropathy coexists; see following discussion). Sensory responses may also be reduced initially in association with sepsis and increase during clinical recovery [8]. Needle electrode examination shows fibrillation potential activity in resting muscle in some patients. On voluntary muscle activation, motor unit potentials are short in duration and polyphasic in form with early recruitment, but when there is severe weakness or encephalopathy due to sepsis, the patient may be unable to contract muscles sufficiently to permit analysis of motor unit potentials. An interesting observation made of patients with critical illness myopathy, and demonstrated by direct muscle stimulation, is that the condition leads to electrical inexcitability of the muscle membrane [13,14] so that the ratio of nerve-evoked muscle action potential to direct stimulation of muscle is close to 1. In contrast, when weakness stems from severe neuropathy, the ratio of nerve-evoked response to muscle-stimulation–evoked response is less than 1 (and close to 0).

Muscle Biopsy

With a fairly stereotypic clinical presentation, and EMG results typical of a myopathy—often with fibrillation potential activity—the muscle biopsy is usually not necessary to establish the diagnosis of ICU myopathy. When the diagnosis is uncertain, and especially when diseases with specific therapies—such as the Guillain–Barré syndrome—are considered, a muscle biopsy may prove helpful. Biopsy shows muscle fiber atrophy, especially involving the type II fibers; a variable degree of muscle fiber necrosis, the absence of any inflammatory cells; and the hallmark of the disorder: features of a disrupted

intramyofibrillar network that manifests as patchy or complete reduction in myosin–adenosine triphosphatase reactivity in nonnecrotic fibers due to a loss of myosin that may be confirmed immunocytochemically or by electron microscopy [8]. There is a spectrum of histopathological severity ranging from a relatively mild myopathy without major structural damage (designated a cachectic myopathy) to a more severe myopathy with selective thick filament loss, and extending to the most severe manifestation of myopathy characterized by pronounced necrotizing features [6].

Pathophysiology

Myosin loss and muscle fiber necrosis probably contribute to persisting weakness. Myosin loss is characteristic of critical illness myopathy, and is essentially pathognomonic of the disorder. Corticosteroids may cause the loss of myosin, but other factors trigger the process, such as an abnormal neuromuscular junction caused by pharmacologic blockade in ICU patients [7]. Consistent with this hypothesis is the observation that a patient with myasthenia developed loss of myosin thick filaments after receiving high-dose corticosteroids [15], and that in an animal model of dexamethasone treatment plus denervation, there was a severe preferential depletion of thick filaments, leading to a reduction in muscle fiber size [16]. Some patients who are not exposed to administered corticosteroids or neuromuscular blocking agents, but who are systemically ill, often with metabolic acidosis, can also develop the myopathy of intensive care. Acidosis may stimulate glucocorticoid production, lead to an increase in muscle protein degradation, and trigger thick filament loss [7]. Finally, as noted earlier, muscle membrane inexcitability is noted in some patients with the disorder. In an animal model of ICU-related myopathy (rats treated with corticosteroids for 7 to 10 days after denervation of muscle in one leg), intracellular recordings in individual muscle fibers demonstrate that many fibers become unable to generate action potentials [17]. Paralysis appears to be due to abnormal inactivation of sodium channels, which suggests that the myopathy of intensive care may be, in part, an acquired disease of ion channel gating.

Treatment

The treatment of critical illness myopathy is essentially symptomatic: treating the underlying systemic illness and to the extent possible, discontinuing or minimizing corticosteroids and neuromuscular blocking agents. There is emerging evidence that intensive insulin therapy might have a role in reducing the incidence of both critical illness myopathy and critical illness polyneuropathy [18], but hypoglycemia remains a major concern. The experience using this modality was based on specific subgroups, which could limit the applicability of the conclusions, and the diagnosis of myopathy was based on EMG criteria alone and did not include information about clinical measures of muscle strength.

Outcome

If patients survive systemic illness, recovery occurs over weeks to months, depending on severity of the myopathy. In patients whose disease severity was pronounced, a recovery period of many months is to be expected along with the need for tracheostomy and long-term ventilatory support; although some motor recovery ultimately occurs in such patients, it is likely that they will be left with residual long-term muscle weakness and atrophy with compromise in daily function and problems with ambulation [19].

CRITICAL ILLNESS POLYNEUROPATHY

Diagnosis

Patients with critical illness polyneuropathy develop a sensorimotor axon-loss polyneuropathy [20]. Although distal muscles may be affected to a greater extent than proximal muscles, more commonly there is generalized flaccid weakness with depressed or absent reflexes. There is usually distal sensory loss, but pain and paresthesias are not typical features. The cranial nerves are generally spared. Many patients with critical illness polyneuropathy have a concomitant encephalopathy stemming from their underlying multiorgan system failure or sepsis, or both [21].

Risk Factors

Approximately 50% of patients admitted to the ICU with sepsis and multiorgan failure for at least 2 weeks will be found to have EMG evidence for an axon-loss polyneuropathy.

Laboratory Studies

EMG Studies

The most important diagnostic test is the EMG. Nerve conduction velocities are normal or only mildly reduced [21], but the amplitudes of sensory and motor responses are reduced, or even absent. This pattern is typical for axon-loss polyneuropathies rather than demyelinating neuropathies and is helpful in distinguishing critical illness polyneuropathy from the Guillain–Barré syndrome, in which, typically, myelin loss leads to slowing of nerve conduction velocities, conduction block and prolonged distal latencies, and delayed late responses (see following discussion). On needle electrode examination, there are typically features of acute denervation—fibrillation potentials and positive sharp wave activity—and reduced recruitment of motor unit potentials; as in many axon-loss polyneuropathies, there may be more pronounced changes seen in distal compared to more proximal muscles.

Pathophysiology

The polyneuropathy appears to be a complication of the systemic inflammatory response syndrome (SIRS) triggered by sepsis, severe trauma, or burns [22]. It may be induced by impaired microcirculation leading to reduced nerve perfusion and endoneurial edema which leads in turn to nerve hypoxia; the neuropathy may also result to a degree from the deleterious effects of cytokines produced by activated leukocytes [23]. There is also evidence that the acute polyneuropathy in critically ill patients stems in part from an abnormality in nerve excitability, caused by increased sodium channel inactivation (similar to what is found in the myopathy of intensive care), without actual nerve damage. This may underlie the reversibility of weakness that occurs in some affected patients [24].

Treatment

Treatment is essentially symptomatic and supportive and comprises attempts to stabilize underlying critical medical and

surgical conditions with vigorous treatment of sepsis. A recent study reported a 44% reduction in the incidence of critical illness polyneuropathy in mechanically ventilated critically ill patients who received intensive insulin therapy (IIT) to maintain the blood glucose levels between 4.4 and 6.1 mmol per L [23]. A Cochrane review makes clear, however, that the methodology of this and other studies limits the conclusions regarding the role of IIT in patients with either critical illness myopathy or neuropathy, or both [18].

Outcome

Recovery of sensory and motor function occurs over weeks to months, depending on the severity of the neuropathy. In some of the instances of very slow recovery over months, long-term ventilatory support may be required, even after the underlying critical illness has resolved [19].

DIFFERENTIAL DIAGNOSIS

Certain well-known peripheral neuropathies, neuromuscular junction disorders, and myopathies may present with acutely evolving weakness and simulate critical illness myopathy or polyneuropathy [1,2,25]. Among the acute and severe polyneuropathies, the most common is the Guillain–Barré syndrome, discussed in detail in Chapter 175. In brief, two-thirds of patients have had a preceding viral or bacterial syndrome (especially a *Campylobacter jejuni*-related diarrheal illness), an inoculation, or recent surgery. Most patients present with rapidly progressive areflexic paralysis that typically starts in the legs and spreads proximally, and involves the diaphragm in 25% of cases and the facial muscles in more than 50% of individuals. Most have EMG features of an acquired demyelinating polyneuropathy with slowing of nerve conduction velocity, conduction block, prolonged distal latencies, and prolonged or absent late responses, distinguishing Guillain–Barré syndrome from critical illness polyneuropathy. In most patients with Guillain–Barré syndrome, the cerebrospinal fluid (CSF) examination shows an elevation in protein without increased white cells by the second week of the illness, helping to distinguish Guillain–Barré syndrome from critical illness polyneuropathy, in which the CSF findings are normal. Guillain–Barré syndrome, an immune-mediated disorder, responds to plasma exchange or to intravenous γ -globulin, making early recognition essential in an effort to start treatment early and reduce morbidity.

A rare cause of severe neuropathic weakness is acute intermittent porphyria that may present with attacks of abrupt onset of abdominal pain, psychiatric disturbance, and polyneuropathy. It is generally triggered by drugs that induce the hepatic cytochrome-P450 system (diazepam, theophylline, barbiturates); it is characterized by weakness of the bulbar muscles and the diaphragm, has prominent dysautonomia, and EMG findings reveal features of a severe axon-loss polyneuropathy. Diagnosis is suggested by the presence of urinary porphyrin precursors, notably δ-aminolevulinic acid. The neuropathy responds to oral or parenteral carbohydrate loading and to intravenous hematin.

The most important neuromuscular junction disorder causing acute weakness is myasthenia gravis, described in Chapter 176. In brief, in this immunoglobulin-G immune-mediated postsynaptic condition, in which there is a loss of acetylcholine receptors, most individuals present with ocular muscle weakness (manifested as ptosis and diplopia) and generalized weakness with a fatigable component. More than 90% of patients have antibodies to the acetylcholine receptor, and abnormal EMG findings, with a decremental motor response during repetitive nerve stimulation at 2 to 3 Hz. The acute weakness (defined as myasthenic crisis when respiratory muscles are involved) responds well to plasma exchange or intravenous γ -globulin.

Another neuromuscular junction disorder is prolonged neuromuscular blockade by muscle relaxants. It is virtually always seen in the population of patients with renal or hepatic failure, is often associated with elevated levels of the metabolite of vecuronium (3-desacetylvecuronium), and tends to improve after infusion of acetylcholinesterase inhibitors. Botulism is a presynaptic disorder characterized by rapidly progressive, diffuse, symmetrical weakness with a proximal predominance, dysarthria and dysphagia, respiratory involvement, and a prominent autonomic component including dilated pupils, bradyarrhythmia, orthostatic hypotension, and urinary retention. Management consists of supportive care and administration of trivalent antitoxin.

THE DIAGNOSTIC CHALLENGE: DISTINGUISHING CRITICAL ILLNESS MYOPATHY FROM CRITICAL ILLNESS POLYNEUROPATHY

Favoring the diagnosis of myopathy would be severe generalized weakness, with failure to wean from mechanical ventilation (the latter more likely to be associated with ICU myopathy rather than neuropathy [26]), preservation of reflexes and sensation, a transient rise in CK, and an EMG picture of relatively preserved sensory responses with low or absent motor responses and early recruitment of small, polyphasic motor unit potentials, often with fibrillation potential activity. Favoring a polyneuropathy would be the clinical findings of demonstrable sensory loss and areflexia, and the EMG findings of absent or low motor amplitudes in the company of absent or low sensory responses, along with fibrillation potentials and reduced recruitment of motor unit potentials. Clinically, a polyneuropathy might easily be missed because, in many patients, careful sensory examination is impossible in the ICU setting, especially if there is a coexisting encephalopathy. Further confounding the distinction, reflex loss can occur in either critical illness polyneuropathy or myopathy, fibrillation potentials may be found in both disorders, and voluntary motor unit potentials may not be elicitable either because of inability to activate muscles due to encephalopathy or from severe weakness.

In the final analysis, it may be difficult to distinguish one disorder from another in an individual case: ICU-related myopathy and polyneuropathy arise in a common setting, share the clinical features of severe generalized weakness with areflexia, may have a similar underlying acquired sodium channelopathy (affecting multiple sodium channel isoforms in both nerve and muscle [24]), and cannot always be reliably differentiated by EMG testing. Although a biopsy may be helpful in ambiguous situations, truly distinctive features of either disorder may be difficult to discern. It is likely that in many patients *both* disorders are present in varying degrees [27] and in fact have a combined syndrome of critical illness myopathy and polyneuropathy and may be considered to have critical illness polyneuromyopathy [5] or critical illness myopathy and neuropathy [6]. Personal and collective experience [14,25,28] suggests that in ICU patients with the *most profound weakness and failure to wean,* ICU myopathy probably plays the predominant role.

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STEPHANIE M. LEVINE

CHAPTER 181 ■ IMMUNOSUPPRESSION IN SOLID-ORGAN TRANSPLANTATION

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Clinically successful solid-organ transplantation required breakthroughs in our understanding of immunology and immunosuppressive therapy. Alexis Carrel, in the early 1900s, described what was to become the modern method of vascular suturing; experimental transplants soon followed [1], but the first successful clinical transplant was not done until five decades later. During that interval, it gradually became apparent that early rapid destruction of allografts was due to an immune process, which came to be known as *rejection*.

Organ transplantation has now become commonplace as the results have improved remarkably with the use of more potent and specific immunosuppressive agents. Progress in nonrenal transplantation has especially accelerated with the use of newer and more potent immunosuppressive agents. Besides the developments in techniques and immunosuppression protocols, progress in tissue typing and cross matching, and in preservation and transportation of harvested organs have played major roles in the rapid development of organ transplantation.

This chapter reviews the clinical use and the adverse reactions associated with commonly used immunosuppressive agents.

PHARMACOLOGIC AGENTS

Calcineurin Inhibitors

Cyclosporine (CSA) and tacrolimus (TAC), although structurally dissimilar, have a similar mechanism of action. Both drugs interfere with the cellular pathway for cytokine production and proliferation. Early events in the T-cell activation process are associated with a rise in the levels of intracellular calcium. The protein calcineurin has been validated as part of the calcium-dependent signal transduction pathway of interleukin-2 (IL-2) production in T cells [2]. CSA and TAC bind to two intracellular receptors, CypA and FKBP12, respectively; these receptors are found in virtually all cell types. The resulting receptor complex binds to calcineurin, blocking its phosphatase ability and thereby stopping the production of IL-2 [2].

The two calcineurin inhibitors (CNIs) currently used are described separately in the following sections.

Cyclosporine

CSA was isolated from a soil sample in Norway and produced by the fungus *Tolypocladium inflatum*. The first formulation of CSA that was approved by the U.S. Food and Drug Administration (FDA) was Sandimmune®; this was modified in the early 1990s by the microemulsion (ME) formulation called Neoral®. In 2000, the first generic versions of CSA were launched. CSA has remained a major component of many transplant regimens.

Pharmacokinetics. CSA is a lipophilic decapeptide, consisting of several amino acids in a ring structure. The original oral formulation (Sandimmune®) is in an olive-oil vehicle, which is necessary to promote absorption [3]. Absorption of Sandimmune® is erratic and it requires the presence of bile in the upper small intestine for absorption. Because many liver transplant recipients require diversion of bile to external drainage, absorption of Sandimmune® is problematic for them [4]. Absorption is also complicated by the presence of food and the length of drug therapy. Neoral® self-emulsifies in water, making absorption much more reliable and much less dependent on the presence of bile.

Studies comparing the two formulations showed these advantages with the ME: a more consistent and linear elimination of CSA; higher area-under-the-curve (AUC) values, leading to reduced dose requirements; reduced effects of diet, and, especially for liver recipients, much better absorption [4]. The side effect profiles were unchanged. The ME has become the primary formulation for CSA. CSA is generally considered a narrow-therapeutic-range drug, so whether generic versions can be used without additional pharmacokinetic study has been controversial.

The oral bioavailability of the ME formulations is approximately 30%. The average half-life of CSA ranges from 6 to 9 hours, with a t_{max} (ME) of approximately 1 hour. CSA is highly bound in plasma to red blood cells. It is extensively metabolized by the liver to multiple metabolites via the cytochrome P450 3A4 enzyme system; however, most of the metabolites are considered essentially inactive. Significant liver impairment can slow the clearance of CSA by the body. Because very little drug is eliminated by the kidney, renal failure does not change CSA elimination [3].

CSA is available as an oral soft gelatin capsule (Neoral®, Sandimmune®), as an oral solution (Sandimmune®, Neoral®), and as an intravenous (IV) preparation (Sandimmune®). To convert to IV use, the IV dose must be calculated as one-third of the daily oral dose. The IV dose can be administered over 6 hours; however, a continuous infusion is usually desired to minimize toxicity.

Adverse Events. The extensive side effect profile of CSA has long been a reason for attempts at minimizing drug exposure. Of most concern is its acute and chronic nephrotoxicity. Acute nephrotoxicity from CSA initially is characterized by vasoconstriction of the intrarenal arterioles, resulting in a reduced glomerular filtration rate. This mechanism of vasoconstriction is not well understood, but may be a result of increase in the vasoactive substance endothelin I [5], the activation of the renin-angiotensin system resulting in increased levels of angiotensin II [6], and possibly a decrease in production of nitric oxide [7]. CSA may also affect prostacyclin levels and induce vasoconstriction by increasing thromboxane A_2 [3].

CSA-induced thrombotic microangiopathy (TMA) was first reported in liver allograft recipients, then in kidney and heart recipients [8]. TMA can present as a full-blown syndrome consisting of hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal failure. Pathogenic mechanisms include a direct cytotoxic effect on endothelial cells, reduction in prostacyclin synthesis leading to vasoconstriction, platelet aggregation, and thrombus formation. CSA reduces the generation of activated protein C from endothelial cells and increases thromboplastin production from mononuclear and endothelial cells, thus contributing to a prothrombotic effect. Discontinuation of CSA is an important step in management along with plasmapheresis and fresh frozen plasma replacement. TAC or sirolimus (SRL) can be substituted as immunosuppressive agents, although TMA can occur with both these agents.

In heart and lung transplant recipients, the effect of CSA on long-term kidney function has been significant. Kidney biopsies of their native kidneys reveal wrinkling and thickening of the glomerular basement membrane, with some kidneys exhibiting microthrombotic angiopathy and fibrosis. Clinical findings showed that several of these recipients had advanced to end-stage renal disease requiring dialysis; others developed significant proteinuria [9]. However, a study of kidney recipients showed that the incidence of rejection correlated with poorer long-term graft function; higher CSA levels were associated with better, not worse, graft function [10]. Whether or not higher CSA levels are to blame for chronic CSA nephrotoxicity is still a matter of discussion. Transforming growth factor-B type 1 (TGF-B type 1) and platelet-derived growth factor, both fibrogenic cytokines, are produced in increasing amounts by human renal proximal tubular cells by increasing concentrations of CSA [11]. An increase in the activation of the renin-angiotensin system has been linked with the morphological changes that occur in chronic CSA nephrotoxicity by experimental studies [12], and angiotensin II receptor blockers reduce these changes.

Hypertension is another significant adverse event with CSA. Most patients receiving CSA develop hypertension, sometimes requiring multiple drug therapy. The mechanism for CSA-induced hypertension is primarily related to small-vessel vasoconstriction. The renal vasoconstriction may be affected, in part, by increased endothelin production. Patients also develop sodium retention and lower plasma renin levels [13]. Treatment of hypertension has focused on calcium-channel blocker use, because calcium-channel activation induces endothelin vasoconstriction and increases blood pressure. Calcium-channel blockers, such as diltiazem, nifedipine, and amlodipine, have been shown to decrease renal vascular resistance and improve glomerular filtration rate. Given these beneficial renal effects, calcium-channel blockers have been used to try to reduce chronic nephrotoxicity associated with CSA. Clinical evidence of a salutary effect has been conflicting, and further study is needed.

CSA has been associated with several neurologic toxicities, including headaches, tremors, seizures, and encephalopathy. In most instances, but not always, these effects are seen with higher CSA levels. A decrease in dosage may prevent serious tremors and headaches. Reversible posterior leukoencephalopathy can occur after CSA use and affects the posterior white matter and the frontal lobes and gray matter as well [14]. It manifests with confusion, coma, cortical blindness, cerebellar syndrome, hemiplegia, and flaccid paralysis or various combinations of these features. This neurological syndrome and brain imaging abnormalities usually resolve within 2 weeks of stopping CSA, or after dosage reduction if blood levels were high [15]. Hypertrichosis and gingival hyperplasia can reduce patient compliance to CSA. Many patients develop hair growth on their backs and arms; although not life threatening, these cosmetic changes can have emotional and physical repercussions, potentially resulting in graft loss if noncompliance ensues. Electrolyte imbalances may occur with CSA, including hyperkalemia, hyperuricemia, and hypomagnesemia. Patients usually need diet instruction and sometimes electrolyte replacement to control these changes. CSA can increase cholesterol and triglyceride levels, sometimes requiring treatment with lipid-lowering medications [3].

Drug Interactions. CSA is metabolized by the cytochrome P450 3A4 enzyme system that is found not only in the liver but also in the cells lining the intestine; so CSA levels can be increased or decreased by changes in gut absorption or in liver metabolism [16]. Some centers try to manipulate the interaction, intentionally using compounds that inhibit CSA metabolism to decrease the dosage required and, thus, the cost [17]. This practice is controversial, because any change in the interacting drug used affects CSA levels. CSA interactions may also occur with medications that change gut motility and with other nephrotoxic agents [16]. Table 181.1 lists the drugs that affect CSA metabolism, efficacy, and nephrotoxicity.

Clinical Use. CSA was and continues to be extensively used in organ transplantation, especially renal transplant, although now a different CNI, tacrolimus, has become the more commonly used primary immunosuppressive agent [18]. When CSA is used, it is often the ME formulation (Neoral®),

TABLE 181.1

SIGNIFICANT DRUG INTERACTIONS (CYCLOSPORINE, TACROLIMUS, SIROLIMUS)

Inhibitors of metabolism	Inducers of metabolism	Additive nephrotoxicity (cyclosporine and tacrolimus only)
Verapamil	Rifampin	Aminoglycosides
Diltiazem	Phenobarbital	Salicylates
Fluconazole	Phenytoin	Nonsteroidal anti-inflammatory agents
Itraconazole	Carbamazepine	
Ketoconazole	St. John's wort	
Erythromycin		Amphotericin B
Azithromycin		Vancomycin
Clarithromycin		
Grapefruit juice		
Fluvoxamine		
Nefazodone		
Atorvastatin		

although patients with stable allograft function from earlier years may still be using Sandimmune. As Sandimmune® and ME formulations are not considered bioequivalent by the FDA, one cannot be substituted for the other without careful monitoring of doses and serum concentrations. Most centers initiate CSA therapy at 4 to 8 mg per kg per day orally, starting the day after transplant. If the transplanted kidney shows signs of acute tubular necrosis posttransplant, some centers may delay the initiation of CSA. Anti–T-cell preparations may be used during this time to provide T-cell suppression if CSA cannot be started [3]. Because of the better bioavailability of the ME formulation, the need for IV CSA has decreased but still may be necessary if the patient has significant diarrhea or cannot tolerate any oral or nasogastric medications.

Therapeutic Drug Monitoring. Monitoring CSA levels is vital. Maintaining the appropriate levels in the first 6 months posttransplant has a significant effect on graft survival [19]. Monitoring CSA is a challenge because of the differences in bioavailability between patients, the narrow therapeutic range, and the number of compounds available that affect CSA blood concentrations. Several different assays are currently in use to measure CSA. The various methods used today measure whole-blood CSA levels and include radioimmunoassay (RIA), high-performance liquid chromatography (HPLC), and monoclonal antibody assays. HPLC only measures the parent compound of CSA, whereas radioimmunoassay and the monoclonal assays measure CSA plus several metabolites. When deciding whether a blood concentration is appropriate, it is important to know which assay the laboratory is using.

Traditionally, trough concentrations (C0) of CSA have been used to determine the appropriateness of a dosing regimen. Earlier studies were performed with the Sandimmune® formulation, which had quite variable dose-response curves. After the use of the ME preparation became standard, several studies suggested that measuring the AUC would be more predictive of toxicity and rejection (compared with the C0) [20]. AUC monitoring requires more blood samples per measurement, and it is therefore more costly and impractical in clinical practice [20]. A monitoring strategy measuring AUC for the first 4 hours after dosing (AUC 0 to 4 hours) correlates well with clinical outcomes, although it still requires multiple blood samples [21]. A blood sample taken 2 hours after intake of Neoral® (C_2) is the most accurate one-point predictor for AUC 0 to 4 hours and shows less variability than either C0 or C_1. In retrospective analysis, the risk of acute rejection is reduced in patients in whom C_2 were greater than 1,500 µg per L in the 2 weeks following transplantation [22].

In a prospective study, 45% of C_2-monitored patients failed to reach the target levels by day 5 posttransplantation compared with 2.5% of Co-monitored patients [23]; this may explain why the theoretical benefit of C_2 monitoring in the early posttransplant period is not borne out. Due to the lack of prospective evidence showing an advantage for C_2 monitoring in the early posttransplant period, trough levels (C0) remain the standard.

Tacrolimus

With the success of CSA, researchers studied soil samples from around the world, looking for another compound that might turn out to display immunosuppressive properties. TAC, initially known as FK-506, was isolated from a soil sample in Tsukuba, Japan, in May 1984, from the fungus *Streptomyces tsukubaensis* [24]. It has a completely different chemical structure from CSA, yet its effect on the lymphocyte is remarkably similar. A few differences have been found on the cellular level between CSA and TAC. The FKBP12-TAC complex is 10 to 100 times as potent as CSA, possibly due to greater affinity for its binding protein [24,25].

Pharmacokinetics. The pharmacokinetics of TAC are similar to CSA. TAC has an extremely lipophilic, macrocytic lactone structure. Its oral bioavailability ranges anywhere from 4% to 93% (average 25%), with variable dose-response curves between patients. Because of this poor oral bioavailability, the IV dose should be calculated at approximately one-third of the oral daily dose [26]. One significant difference between CSA and TAC is that with TAC the presence or absence of bile in the digestive tract does not significantly alter absorption. This was a problem with Sandimmune® and a reason that TAC was initially studied in the liver transplant population. TAC binds extensively to erythrocytes and exhibits the same temperature-dependent properties as CSA. The metabolism is also similar to CSA, with the cytochrome P450 3A4 system as the primary metabolic pathway. The many metabolites for TAC are still being studied. Less than 1% of active drug is excreted through the urine. The average elimination half-life ranges from 8 to 20 hours, depending on the population studied [26].

TAC is available as a 0.5-mg, 1.0-mg, and 5.0-mg capsule, formulated as a solid dispersion in hydroxymethylcellulose. A suspension can be compounded if necessary for pediatric or nasogastric administration. An IV preparation is solubilized in alcohol and a surfactant. It is available as a 5 mg per mL concentration that must be diluted and administered as a continuous infusion to avoid toxicity [26].

Adverse Events. The adverse event profile of TAC is similar to CSA in many respects. TAC appears to have the same nephrotoxicity seen with CSA, and the mechanism also appears to be the same. However, in one study, mean or median serum creatinine levels in renal transplant recipients were lower in TAC-treated patients, with 5 years follow-up, than in patients treated with cyclosporine ME (or standard formulation) [27]. As with CSA, the nephrotoxicity of TAC is concentration dependent, making drug level monitoring equally important [28].

Hypertension has also been reported with TAC. However, the 5-year follow-up results from the U.S. randomized trial indicate that significantly fewer TAC than CSA recipients were receiving antihypertensive treatment (80.9% vs. 93%, $p < 0.05$) [27]. Immunosuppression with TAC-based regimens is associated with better lipid profiles than is immunosuppression with CSA-based regimens [29]. Neurotoxicity appears to be somewhat worse than with CSA. In randomized trials, liver recipients had more trouble with the neurotoxicity of TAC versus CSA, even when controlling for previous liver failure–induced encephalopathy [30]. Headache, tremor, neuropathy, seizures, blindness, coma, and various other neurologic complaints have been seen with TAC [30]. Patients usually recover when the drug is stopped. The incidence of hyperkalemia appears to be similar to that with CSA, although hypomagnesemia is more likely to occur with TAC-treated patients [31].

TAC-associated TMA has a reported incidence between 1% and 4.7% [32]. All patients have an elevated serum creatinine, but do not always show signs of hemolysis. Renal allograft biopsy provides a conclusive diagnosis. Treatment consists of reduction or discontinuation of TAC, anticoagulation, and/or plasmapheresis with fresh frozen plasma exchange and leads to resolution of TMA in most instances. Rarely, there may be loss of kidney function or patient death.

The incidence of posttransplant diabetes mellitus (PTDM) was significantly higher among TAC-treated patients than CSA-treated patients (9.8% vs. 2.7%) according to a meta-analysis [33]. Many patients with PTDM have reversal of diabetes mellitus, with eventual discontinuation of insulin. In a U.S. trial combining TAC with mycophenolate mofetil (MMF) and corticosteroids, the 10-year incidence was 6.5%, and the 1-year prevalence was 2.2% [34]. TAC does not appear to cause hypertrichosis or gingival hyperplasia, but instead is associated

with hair loss. Sometimes these differences become important enough to cause a change in therapy.

Drug Interactions. TAC is metabolized through the same pathway as CSA and has been subject to the same interactions with the cytochrome P450 3A4 system. If the medication is known to alter P450 3A4 activity, it probably alters TAC concentrations. Drugs that cause nephrotoxicity also have the same additive effects with TAC as with CSA (Table 181.1).

Therapeutic Drug Monitoring. As with CSA, careful blood concentration monitoring is required; TAC also has a narrow therapeutic range. TAC is extensively bound to erythrocytes, so whole-blood trough measurements have become the standard for drug monitoring. The primary assay used currently is an automated microparticle enzyme immunoassay, available from Abbott Laboratories (Abbott Park, IL). Several generations of this assay have been used, with the current assay more sensitive at lower drug concentrations. The current suggested therapeutic range for TAC is 5 to 20 ng per mL; however, this range is still controversial and under study [25].

Clinical Use. Because TAC does not require bile to be absorbed, its use has attracted a great deal of interest in liver transplantation. Sandimmune® required bile in the small intestine, and if the bile drainage was being diverted it was almost impossible to obtain adequate CSA blood levels. TAC provided a possible advantage in liver transplantation, so the first major trials were in liver recipients.

The U.S. Multicenter FK-506 Liver Study Group compared the efficacy and safety of a CSA-based regimen (using Sandimmune®) versus a TAC-based regimen in adult and pediatric liver recipients at 12 different centers in the United States [30]. Recipients were randomized to CSA in combination with Azathioprine® (AZA) and steroids, or to TAC in combination with steroids. The investigators looked at patient and graft survival rates as well as the incidence of acute rejection, steroid-resistant rejection, and refractory rejection. At 1 year posttransplant, patient and graft survival rates were similar between the two groups, but TAC was associated with fewer episodes of all categories of rejection. The TAC group did have an increased incidence of adverse events, including nephrotoxicity, neurotoxicity, and hyperglycemia. Follow-up studies using lower doses of TAC have shown a reduction in these adverse events [35,36].

TAC is usually initiated at a dose of 0.05 to 0.10 mg per kg per day. Some centers use a standard starting dose of 2 mg BID, and adjust doses based on the blood concentration. As with CSA, TAC may be delayed after a kidney transplant in the case of graft dysfunction, and started when the kidney is recovering from acute tubular necrosis.

In studies of TAC and CSA in kidney recipients, results have been similar to those with liver recipients (i.e., same graft and patient survival rates, fewer rejection episodes) [37]. This pattern has also been seen in higher-risk patient populations, such as black recipients [38]. Other transplant categories with historically higher rates of rejection, such as pancreas transplant recipients, have seen benefit with TAC-based immunosuppressive regimens [31]. TAC continues to be the primary maintenance immunosuppressive agent in heart, lung, and bowel recipients, and was approved by the FDA for heart transplantation in 2006 [39–42].

Antiproliferative Agents

Antiproliferative agents have been part of transplant protocols since the first transplant was performed in the 1960s. Early antiproliferative agents included radiation, azaserine, and actinomycin D. AZA, developed in the early 1960s, was part of the first successful transplant series reported in 1963. It continues to be used today in maintenance immunosuppressive regimens and for autoimmune diseases. Cyclophosphamide was used when AZA use was not possible, but because of side effects it has never been considered a suitable alternative. A major advance in antiproliferative agents has been the development and use of MMF, released for clinical use in 1995. MMF is now a component of most new transplant regimens, with AZA having been used in transplants performed before 1995.

Azathioprine

Pharmacology. AZA is actually a prodrug of 6-mercaptopurine, an antineoplastic agent used in leukemia regimens. It acts by the inhibition of purine synthesis in the de novo pathway. This purine inhibition leads to the inhibition of the mixed lymphocyte reaction, and to a lesser extent, the antigen–antibody reaction [43].

Pharmacokinetics. AZA is rapidly absorbed after oral administration, with peak levels occurring 1 hour after ingestion. The large first-pass effect after oral administration means that IV doses must be multiplied by a factor of two. AZA is metabolized by xanthine oxidase through several steps to 6-thiouric acid and excreted into the kidneys. Although the half-life of the parent drug is relatively short, the pharmacodynamic effects of the parent drug and metabolites far outlast the time that AZA is present in the bloodstream [43].

Adverse Events. AZA is relatively well tolerated by most patients. The most common side effect is myelosuppression due to suppression of purine synthesis by AZA. The myelosuppression is usually limited to the white blood cells, but occasionally red cell aplasia is observed. Most patients can tolerate this effect by reducing the daily dosage, although some need to discontinue the drug entirely. Liver function tests must be regularly monitored: AZA has been reported to cause hepatic necrosis and liver failure. Pancreatitis or a skin rash may indicate an allergic reaction, in which case AZA may need to be stopped. Hair loss is bothersome to some patients but is reversible. Gastrointestinal (GI) disturbances, including nausea and vomiting, are mild and usually tolerable [43].

Drug Interactions. Severe pancytopenia has been reported when AZA and allopurinol are used together. It is recommended that AZA doses be reduced by 75% if allopurinol is added to the patient's drug regimen. With the development of MMF, the management of this interaction has become easier, as MMF (which is metabolized differently than AZA) can be substituted for AZA when allopurinol is indicated [43].

Clinical Use. AZA is available as a 50-mg tablet that can be split, if necessary. A compounded suspension of 5 mg per mL can be used if tablets are not an option. AZA is also available IV. Most recipients are maintained on a dose of 1.0 to 2.5 mg per kg per day. AZA has an important historical role in transplantation, but its use has declined as newer agents have been introduced. Most likely, recipients currently on AZA were transplanted before 1995 and have done well on that initial regimen. Some centers switched all their recipients when MMF became available, but many are still maintained on AZA due to a significant cost advantage over MMF.

Mycophenolate Mofetil

MMF was approved by the FDA in 1995 to prevent rejection in kidney recipients. Its use has grown to include liver, heart, lung, and pancreas recipients. It has been a major addition to

the immunosuppressive arsenal. Many centers have replaced AZA with MMF in their current protocols.

Pharmacology. MMF is also a prodrug, quickly metabolized to the active compound, mycophenolic acid (MPA). MPA acts as a noncompetitive inhibitor of inosine monophosphate dehydrogenase, thereby blocking de novo purine synthesis and proliferation in the T and B lymphocytes [44]. In vitro and in vivo data from rodent models of chronic allograft nephropathy suggest that MMF also decreases vascular smooth muscle cell proliferation, offering theoretical treatment possibilities for the morphology seen in chronic rejection [45].

Pharmacokinetics. Oral MMF is rapidly hydrolyzed in the bloodstream by esterases to MPA, with no measurable parent compound in serum [46]. The oral bioavailability for MPA approaches 100%, so the IV to oral conversion ratio is 1:1. IV administration of MMF provides measurable blood levels of the parent compound during infusion, with levels becoming immeasurable 12 minutes after the end of the infusion. Peak concentrations occur approximately 1 hour after IV or oral administration (but IV has a slightly higher peak than oral) [47]. MPA is subsequently glucuronidated in the liver to inactive metabolic mycophenolic acid glucuronide (MPAG). Enterohepatic cycling recirculates a significant percentage of MPAG secreted in bile back to MPA, displaying a secondary peak in plasma MPA concentration [48]. MPAG is eventually excreted, primarily in the urine; only 6% of MPAG is excreted in the feces [44].

Adverse Events. MMF can cause significant GI problems, including nausea, vomiting, diarrhea, abdominal pain, and gastroesophageal reflux. Persistent diarrhea not accompanied by fever may be associated with an erosive enterocolitis causing malabsorption of nutrients that has been attributed to a toxic action of the acyl MPAG metabolite on absorptive cells [49]. Occurrence of these side effects has more frequently been linked to the MMF dose rather than to the plasma concentration of parent compound or its metabolites. Dividing the total daily dose into four doses instead of two has been effective in reducing GI problems in some recipients. An alternative, enteric-coated form of MPA—mycophenolate sodium (EC-MPS)—has been developed to mitigate the GI toxicities. Patients who had GI intolerance on MMF administration required fewer dose changes of EC-MPS, and showed reduced symptom burden, better functioning, and improved health-related quality of life [50]. Neutropenia and thrombocytopenia can also occur with MMF, requiring a dosage reduction [44]. At 2 g per day, the occurrence rate in the major trials was comparable to AZA. Teratogenic trials of MMF in rabbits showed changes in offspring at doses equivalent to those given to humans. No human teratogenic trials have been performed (but the manufacturer recommends that female patients wait at least 6 weeks after stopping MMF before trying to conceive). Female healthcare workers are also advised by the manufacturer to not open capsules for fear of aerosolization of the drug. It is also recommended that IV MMF be administered using standard chemotherapy precautions [51].

Drug Interactions. MMF is not metabolized by the cytochrome P450 system; therefore, interactions with MMF only affect its absorption, enterohepatic cycling, or renal excretion. As discussed earlier, a significant percentage of the AUC for MMF comes from enterohepatic cycling. Cholestyramine, a bile acid resin, decreases cholesterol by interfering with its enterohepatic cycling. The mixture of cholestyramine and MMF decreases the total AUC by 40%, so the combination of these two drugs is not recommended [51]. Antacids appear to reduce absorption of MMF by 20%, so adjusting dosing times, if possible, is recommended. Ganciclovir and acyclovir compete with MPAG for secretion by the kidney, and animal studies have suggested a possible interaction [51].

Recipients treated with CSA in combination with MMF display lower MPA concentrations than do patients who are not receiving CSA [52]. However, coadministration of MMF with TAC tends to increase MPA levels due to the lack of CSA inhibitory effects, and also possibly due to the inhibition of the uridine diphosphate—glucuronosyl transferase that generates MPAG [53].

Clinical Use. The success of MMF has allowed it to generally replace AZA in many transplant centers. The results of three major trials were instrumental. The U.S., Tricontinental, and European trials compared MMF, in combination with CSA and steroids, with conventional immunosuppression. The U.S. and Tricontinental trials randomized patients to MMF at a low (2 g per day) or high dose (3 g per day) versus AZA, whereas the European study used a placebo instead of AZA [54–56]. All three trials saw significantly reduced rejection in the MMF arm at 6 months posttransplant. The low-dose and high-dose arms demonstrated significantly fewer rejection episodes and clinically significant reductions in the severity and treatment of rejection episodes. Whether long-term MMF changes survival rates is still controversial. The 3-year data from the U.S. trial periods do not yet show a statistically significant difference in patient or graft survival [53].

The high dose (3 g per day) was associated with more side effects in all three trials. Patients on the high dose developed more infections and had a higher rate of GI intolerance and marrow suppression [54–56]. FDA approval of MMF was at a starting dose of 2 g per day, given as a divided dose of 1 g twice daily. In recipients who develop GI or hematologic toxicity, the dosage should be reduced or MMF should be withheld for a few doses. Dividing the daily dose into more than two doses per day can also be beneficial. Recipients may need to discontinue MMF or convert to EC-MPS for GI intolerance.

The major trials used the less effective oil-based form of CSA. A European study using the ME-CSA formulation (Neoral®) showed only modest, insignificant reductions in acute rejection episodes with MMF compared with AZA, questioning the value of using the costlier MMF [57]. These findings which are drawn on low immunologic risk patients ought to be applied cautiously in other situations.

A subgroup analysis of the higher immunological risk African-American patients enrolled in the U.S. pivotal trial showed that the benefit for African-American versus Caucasian recipients was restricted to the MMF 3 g dose versus the MMF 2 g dose or azathioprine cohorts [58]. Thus, African-American recipients should receive 3 g per day unless they are unable to tolerate that dose.

In a multicenter trial, using a combination of TAC with MMF, a MMF dose of 2 g per day reduced the incidence of acute rejection episodes compared with MMF 1 g per day or AZA—the low acute rejection rate of 8.6% using a combination with MMF 2 g per day suggest that a combination with TAC produced superior results to a combination with CSA [59].

Therapeutic Drug Monitoring. Based on initial pharmacokinetics studies, MMF doses have not been calculated on a milligram per kilogram basis [47]. However, there exists a rationale to implement therapeutic drug monitoring for MMF, as pharmacokinetic variability of MMF has been documented due to differences in hepatic/renal function, concurrent drug administration, and the presence of diarrhea, but not to ethnicity [60]. It is the MPA parent compound and not the parent drug MMF that is readily measured in plasma by HPLC, owing to its high predose concentration (C0). Full MPA AUC monitoring with at least seven samples is impractical on a

routine basis. Concentration monitoring is most useful early after transplantation when absorption may be slow and incomplete, and clearance more rapid than at 3 months [61].

Sirolimus

The newest immunosuppressive agent to be released by the FDA belongs to a class of compounds known as the mammalian target of rapamycin (mTOR) inhibitors. Sirolimus (SRL), formerly known as rapamycin, was approved in September 1999 to prevent rejection in kidney recipients. It is produced by *Streptomyces hygroscopicus*, a fungus isolated from a soil sample found on Easter Island (Rapa Nui). SRL is the first mTOR inhibitor to be approved in the United States. A derivative of rapamycin, everolimus, was approved by the FDA in August 2004.

Pharmacology. SRL binds to FKBP-12, the same binding protein as TAC. It was initially thought that SRL and TAC could be antagonistic, given that they shared the same binding protein. Further research revealed, however, that the target of SRL is not calcineurin, but rather the target protein mTOR [62]. The inhibition of mTOR prevents cell-cycle progression from G1 to S in T lymphocytes; thus, SRL blocks the rejection pathway at a later stage than CSA or TAC [63].

SRL, because of its inhibition of lymphocyte proliferation at a later stage, may work synergistically with CSA or TAC. Median effect analysis of the pooled data to demonstrate immunosuppression synergy between CSA and SRL shows that administration of SRL allows a twofold reduction in CSA exposure, and conversely CSA allows a fivefold reduction in SRL dose to achieve the same immunosuppressive efficacy [64]. However, SRL reduces the exposure to TAC when the two drugs are coadministered [65].

Pharmacokinetics. SRL is rapidly absorbed, but the systemic bioavailability of the current formulation is approximately 15%. Food can affect systemic absorption, and SRL should be taken consistently with a meal. SRL is extensively distributed among blood components, but unlike CSA or TAC the distribution does not appear to be temperature dependent [66,67]. Only a small fraction of SRL remains unbound. It is extensively metabolized, with seven major metabolites currently identified. The primary pathway for metabolism is the cytochrome P450 3A4 enzyme system. SRL has a much longer half-life than CSA or TAC, with an average terminal half-life of approximately 60 hours. This extended half-life allows it to be dosed on a once-a-day basis. Hepatic impairment can extend the elimination half-life, so patients with mild to moderate liver disease may require dosage adjustment [67].

SRL is currently available as a 2 mg and 1 mg tablet and as a 1 mg per mL suspension. The tablets should not be crushed. For administration, the suspension should be mixed only with water or orange juice; no other liquids have been tested. No IV formulation is commercially available [68].

Adverse Events. SRL has a different profile of adverse events than other immunosuppressive drugs. In one study, SRL used alone in kidney recipients resulted in a lower serum creatinine level and a higher glomerular filtration rate, compared with CSA [68]. SRL use is not entirely bereft of adverse effects on the kidney. TMA has been found to occur with the use of SRL in the absence of CNI use [69]. Proteinuria is a common manifestation of SRL toxicity in patients converted from CNI for renal impairment. Pre-existing renal damage may be necessary before proteinuria manifests [70]. In such cases, proteinuria resolves when patients were converted back to CNI and SRL was stopped [71]. Delayed recovery from ischemia–reperfusion injury has been observed in registry analysis [72] and this occurs due to inhibitors of cell proliferation by SRL affecting tubular repair [73].

Hypertriglyceridemia and hypercholesterolemia are dose-related adverse events of SRL that may be exacerbated by the use of steroids or CNI [74,75]. Their effect appears to peak after 1 month of SRL therapy; in some recipients, lipid levels decreased to near baseline concentrations after 1 year. Fifty-three percent of SRL-treated patients required lipid-lowering agents compared with 24% in the CSA group. The increase in lipids seen with mTOR inhibitors is a long-term concern.

SRL causes dose-dependent thrombocytopenia and leukopenia, particularly during initial therapy; their incidence is variable and usually self-limiting. Significant decreases in platelet or white blood cell counts can be treated by decreasing the dosage. Occurrence of leukopenia and thrombocytopenia correlates with SRL trough concentrations greater than or equal to 16 ng per mL [76]. The incidence of anemia is also increased with the use of mTOR inhibitors. In the global study of primary use of SRL in renal allograft recipients, anemia was observed in 16% of recipients taking 2 mg per day and 27% of recipients taking 5 mg per day of SRL [77].

During clinical trials, other adverse events associated with SRL included hypertension, rash, acne, hypokalemia, diarrhea, aphthous ulcers, and arthralgias [67]. Thirty-one cases of interstitial pneumonitis were reported by the FDA [78], which can occur any time after initiation of SRL treatment and can progress to respiratory failure. A mortality of 12% was noted in this report, although early recognition with immediate discontinuation of SRL should reduce mortality.

Other adverse effects that occur with de novo SRL use in kidney recipients include wound healing problems and lymphoceles [79]. A systemic program based on patient selection with body mass index < 32 kg per m^2, the use of closed suction drains, modifications of surgical technique, and avoiding a loading dose of SRL led to a reduction in wound complications and in the incidence of lymphoceles.

Drug Interactions. Most of the drug interactions that have been reported for SRL are related to P450 enzyme inhibition or induction—the same list of drugs that interact with CSA and TAC. Any compound that can affect P450 metabolism may also affect SRL metabolism. As mentioned earlier, significant changes in exposure to TAC or CSA can occur when prescribed along with SRL.

Patients taking SRL have a much higher exposure to MPA, the active constituent of MMF, than do patients taking CSA and MMF [80]; a similar drug interaction is recognized for TAC as well.

Clinical Use. The phase II trials conducted in Europe were among the earliest that used SRL as a principal immunosuppressant. Pooled data from two of these studies showed significantly higher glomerular filtration rates in patients receiving SRL as compared to CSA [81]. A systematic review of randomized trials in which mTOR inhibitors were used in place of CNI as initial therapy after kidney transplantation revealed no difference in the incidence of acute rejection at 1 year, but the serum creatinine was lower in patients receiving mTOR inhibitors [82]. The two large phase III studies of SRL, one conducted in the United States [83] and the second worldwide [77], revealed much about how best to use SRL and its drawbacks. There was a higher incidence of lymphocele formation and wound infection in the SRL arm compared with the control arm. It was also found that the renal function of patients on a combination of SRL and CSA was worse than patients on CSA alone. Regarding the combination of SRL with TAC, registry data suggest poorer graft survival compared to the combination of TAC with MMF [84]. Phase III studies indicated that the combination of either 1.5 mg per day or 3 mg per day of everolimus was better than MMF in the prevention of acute renal allograft rejection when combined with CSA and steroids after kidney transplantation.

The combination of everolimus/CSA was associated with poorer renal function than MMF/CSA combination [85].

Inhibitors of mTOR are potentially attractive agents for use in the maintenance phase of the posttransplant course in patients with CNI toxicity and as a later addition to CNI to enhance immunosuppression in response to acute rejection. A randomized controlled trial suggests that conversion to SRL with impaired graft function results in a rapid improvement in measured glomerular filtration rate at 3 months that was sustained at 2 years; patients remaining on CNI experience deteriorating graft function [86]. Time for conversion in such patients is unclear, but early rather than late conversion is probably best, before the structural changes associated with interstitial fibrosis/tubular atrophy become extensive [87].

Inhibitors of mTOR are known to prevent tumor cell growth. Temsirolimus, an SRL derivative, has been used in phase I/II clinical trials of advanced renal carcinoma, breast cancer, prostate cancer, pancreatic cancer, glioblastoma, and lymphoma. A multivariate analysis of posttransplant malignancies in renal allograft recipients showed a lower incidence of malignancy in patients taking mTOR inhibitors alone or in combination with CNI compared to those taking CNI alone [88]. SRL has been also found to be effective in the treatment of posttransplant lymphoproliferative disorder (PTLD) [89] and Kaposi's sarcoma [90].

Therapeutic Drug Monitoring. Drug level monitoring is extremely important, especially in newer protocols that may not contain CNI or steroids. Making an accurate assay commercially available has been difficult, hindering use of the drug in some instances. Research is ongoing to determine the best assay system. HPLC has been studied and is being used in several centers with good success to date [75]. An immunoassay is also available for SRL therapeutic drug monitoring.

Initial therapeutic drug monitoring of SRL has correlated well with trough concentrations and allograft rejection, such that trough concentrations are generally accepted as a good measure of SRL activity. The therapeutic range is still being debated, but the general agreement is that concentrations between 5 and 15 ng per mL will prevent rejection and toxicity in most patient populations. Higher-risk patients may need to achieve higher trough concentrations [75].

Corticosteroids

Steroids have been a part of transplantation since its inception. It soon became clear, however, that the toxicities of steroids could overshadow their benefits. The role of steroids in transplantation is changing, as experience is gained in the use of newer immunosuppressive medications that are serving to limit corticosteroid use.

Pharmacology

Steroids have many different effects on the immune system. They inhibit T-cell proliferation, T-cell–dependent immunity, and the expression of various cytokines, especially IL-2, IL-6, interferon-γ , and tumor necrosis factor-α (TNF-α) [91]. They also suppress antibody formation and the delayed hypersensitivity response found in allograft rejection [92].

Clinical Use

For years, steroids have been part of any immunosuppressive regimen to prevent and treat rejection. For use in standard immunosuppression, recipients typically begin on a high initial dose [anywhere from 1 mg per kg to 500 mg IV of methylprednisolone (MP)] on the day of the transplant, and then taper over weeks to months to their final maintenance dose. Most centers maintain recipients on 5 to 10 mg daily or every other day. PRED is the oral drug of choice in most programs; however, if IV dosing is required, MP is the drug of choice. The true ratio of MP to PRED potency is 0.8 to 1.0, although for most recipients that difference is small enough to allow a one-to-one conversion [93].

Steroids at high doses have successfully reversed rejection episodes [94]. Most centers use 500 mg to 1 g of IV MP for three doses to reverse a suspected or documented rejection episode. Recipients should be advised that the typical adverse effects for steroids may be magnified at these higher doses. Many centers use three doses of IV MP for mild to moderate rejection episodes. Antibody therapy is used for steroid-resistant rejection or high-grade rejection.

Adverse Effects

Steroid use is associated with a number of problems, acute and long-term. Acute toxicities of corticosteroids include sodium retention, glucose intolerance, mental status changes, and increase in appetite, acne, and gastritis. Most of these problems are magnified with higher doses and are reduced or eliminated once the dosage is reduced. The long-term side effects are costly to treat and reduce quality of life. A cost estimate for the incidence of cataracts, hypertension, osteoporosis, and diabetes in transplant recipients was in the range of $2,500 to $7,500 per patient over 10 years [95]. Graft loss due to rejection is being replaced by death with function, a term referring to recipients who die with a functioning graft. Cardiovascular disease has become one of the leading causes of death with function. Hypertension, hyperlipidemia, and steroid-induced diabetes may be partly responsible for increasing the risk of cardiovascular death. Accordingly, many transplant centers are switching to steroid-withdrawal/steroid-free protocols for many of their recipients.

Steroid Withdrawal Protocols. A meta-analysis of trials where steroid withdrawal had been done in the first year after kidney transplantation showed that although the risk of acute rejection was more than twofold when steroids were withdrawn, there was no significant difference in the incidence of graft failure [96]. Although four of the trials used MMF/CSA and two used MMF/TAC, no attempt was made to differentiate steroid-sparing potential of CSA and TAC. The European TAC/MMF study group randomly assigned immunologically low-risk patients who had undergone transplantation 3 months earlier to continue triple therapy (TAC, MMF, and steroids), withdraw steroid, or withdraw MMF. Incidence of acute rejection was similar in all three groups at 6 months [97] suggesting TAC enables more effective steroid sparing than CSA. Graft and patient survival and the incidence of acute rejection were similar between groups at 3 years, and serum creatinine levels remained stable [98].

A 3-year analysis of a large trial was done of 300 patients receiving basiliximab induction, CNI, and MMF or SRL in which patients were assigned to have steroids withdrawn on day 2 or to continue steroids. No difference was noted in graft function, patient and graft survival, biopsy proven acute rejection, or chronic allograft nephropathy between the two groups [99]. Use of MMF and SRL, with a CNI, may allow safe withdrawal of steroids earlier.

BIOLOGIC IMMUNOSUPPRESSION

Various antibody preparations, both of polyclonal and monoclonal origin, are currently used in clinical immunosuppression. Polyclonal antibodies directed against lymphocytes were developed first and have been used in transplantation since the 1960s. Monoclonal antibody techniques were discovered later, and, in turn, allowed for the development of biologic agents

such as OKT3, which target specific subsets of cells. A number of different monoclonal antibodies (mAbs) are currently under development or in various phases of clinical testing; several have been tested and are now in clinical use. Many are directed against functional secreted molecules of the immune system or their receptors, rather than against actual groups of cells.

One disadvantage of early murine-based antibody preparations such as OKT3 is the potential for the development of antimouse antibodies by the recipient—antibodies that may then limit further use of the agent. To address this problem, recent efforts have focused on the development of so-called humanized versions of mAbs. One option is to replace the constant Fc portion of the parental murine antibody with a human Fc component, thus creating a chimeric antibody. These mAbs may be further humanized to preserve only the original complementarity-determining region, the hypervariable region of the antibody that determines antigen specificity. The remainder of the original murine mAb molecule is replaced by human immunoglobulin G. The advantages of these humanized mAbs are a very long half-life, reduced immunogenicity, and the potential for indefinite and repeated use to confer effects over months rather than days [100]. Biologics are used as rescue agents in 20% of all acute rejection episodes, whilst 50% to 70% of patients undergoing kidney transplantation receive biologic induction [18].

Polyclonal Antibodies

Polyclonal antibodies are produced by immunizing animals, such as horses or rabbits, with human lymphoid tissue; allowing for an immune response; removing the resulting immune sera; and purifying the sera in an effort to remove unwanted antibodies. What remain are antibodies that recognize human lymphocytes.

Polyclonal preparations consist of a wide variety of antibodies and detect specificities include many T cell molecules involved in antigen recognition (CD3, CD4, CD8, and TCR), adhesion (CD2, lymphocyte function antigen [LFA]-1, and intracellular adhesion molecule [ICAM]-1), and costimulation (CD28, CD40, CD80, CD86, and CD154), and non-T cell molecules (CD16 and CD20), and class I and class II major histocompatibility complex (MHC) molecules.

After administration of these antibodies, the transplant recipient's total lymphocyte count should fall and hence these are known as depleting antibodies. Lymphocytes, especially T cells, are then lysed, cleared from the circulation, and deposited into the reticular endothelial system. Alternatively, their surface antigen may be masked by the antibody. Polyclonal antibodies have been successfully used to prevent rejection and to treat acute rejection episodes. Two main polyclonal antibody agents are available for clinical use in the United States: ATGAM and Thymoglobulin.

The broad reactivity with adhesion molecules and other receptors upregulated on activated endothelium has led to preferential use of polyclonal antibodies in situations with prolonged ischemia times where endothelial activation and ischemic reperfusion injury is expected [101].

ATGAM®

ATGAM® is obtained by immunizing horses with human thymocytes. It is generally administered at a dose of 10 to 15 mg per kg, in a course lasting 7 to 14 days. ATGAM® must generally be infused into a central vein, because infusion into a peripheral vein is often associated with thrombophlebitis. To avoid the cytokine release syndrome, recipients should be premedicated with MP and diphenhydramine hydrochloride. Side effects include fever, chills, arthralgia, thrombocytopenia, leukopenia, and a serum sickness–like illness. These side effects are more likely related to the release of pyrogenic cytokines such as TNF-α, IL-1, and IL-6 which result from cell lysis due to antibody binding to targeted cellular surface receptors [102]. Increased infection rates are associated with all immunosuppressants, but certain infections, such as cytomegalovirus, are more common after the use of ATGAM® and other antibody preparations [103].

Thymoglobulin (ATG-R)

Thymoglobulin is obtained by immunizing rabbits with human thymocytes. Initial kidney transplant studies show ATG-R® to be statistically superior to ATGAM® in preventing acute rejection episodes and in reversing acute rejection episodes [104,105].

ATG-R® induction and reduced maintenance immunosuppression has been used in closely followed patients and resulting in graft and patient survivals comparable to standard triple immunosuppression [106]. Administration before reperfusion is advocated to maximize antiadhesion molecule effects.

Comparison studies showed that OKT3 reversed a slightly higher number of rejection episodes than ATG-R® in kidney recipients, but both were efficient treatments. First-time use of ATG-R® was associated with fewer side effects than OKT3 [107]. The side effect profiles of ATG-R® and ATGAM® are similar. With ATG-R®, leukopenia and thrombocytopenia may be quite significant. If a significant drop in platelets or white blood cells is noted, the dosage should be halved or the drug temporarily withheld.

Monoclonal Antibodies

The hybridization of murine antibody–secreting B lymphocytes with a nonsecreting myeloma cell line produces mAbs. A number of mAbs are active against different stages of the immune response. OKT3® has been the most commonly used mAb, but the last few years have seen the introduction and wide use of a number of chimeric and humanized mAbs. Chimeric antibodies preserve the specificity of the original antibody better, whereas humanized antibodies are less likely to be neutralized [108]. Both strategies are effective in preventing antibody clearance.

OKT3

On binding to CD3, OKT3® mediates complement-dependent cell lysis and antibody-dependent cell cytotoxicity leading to rapid clearance of T cells from the peripheral circulation [100]. Pan-T cell activation before their elimination results in systemic cytokine release, and a marked cytokine release syndrome which results in most of the adverse effects associated with OKT3®.

Along with T cell depletion, the overall effect of OKT3® is likely to be due to interrupted T cell receptor (TCR) binding and internalization, disrupted trafficking, and cytokine-mediated regulatory changes.

The standard dose of OKT3® is 5 mg per day given IV, although smaller doses may be as effective. Efficacy can be measured by monitoring CD3-positive cells in the circulation. If OKT3® is effective, the percentage of CD3-positive cells should fall to, and stay below, 5%. Failure to reach this level indicates either an inadequate dose or the presence of antibodies directed against OKT3®. Human antimouse antibodies may develop in at least 30% of patients, and render OKT3® ineffective, allowing for the reappearance of CD3-positive cells in the circulation. This scenario is more common with retreatment using OKT3® or with prolonged treatment.

OKT3® is highly effective and versatile. Most commonly, it is used to treat biopsy proven acute rejections in patients who have failed 3 days of therapy with high-dose MP [109]. OKT3® has also been used as induction therapy to prevent acute rejection and as primary treatment for acute rejection associated with vasculitis (Banff 2 or 3) [110]. Use of OKT3® as an induction agent has declined due to its side-effects' profile. Significant, even life-threatening, side effects may be seen with OKT3®. They may occur when cytokines (e.g., TNF, IL-2, and interferon) are released by T cells into the circulation. These side effects usually occur relatively soon after infusion of OKT3®, and they tend to be most severe after the first and second dose, generally abating by the third or fourth dose. Premedication with IV steroids and agents such as diphenhydramine hydrochloride is important to try to minimize these side effects. The most common symptoms are fever and chills, which generally occur within 30 to 60 minutes after the infusion. Generally, only symptomatic treatment is needed. If fever persists beyond the third dose, then an infectious cause should be sought.

The most serious side effect with OKT3® is a rapidly developing, noncardiogenic pulmonary edema that can be life threatening. The risk of this side effect significantly increases if the recipient is fluid overloaded before beginning OKT3®. Pulmonary edema may develop even in euvolemic patients. If patients are fluid overloaded, they should undergo dialysis or ultrafiltration to remove excess volume before they begin OKT3®.

OKT3® is associated with a wide spectrum of neurologic complications. The most common side effect is headache. Aseptic meningitis has also been reported, albeit usually self-limiting. In this situation, a lumbar puncture demonstrates leukocytosis, but the fluid is sterile. Encephalopathy, ranging from mild to severe, has also been described. If severe encephalopathy develops, OKT3® should be discontinued.

Nephrotoxicity occurring with OKT3® therapy is usually self-limiting, and the recipient improves after the first few doses. Allograft thrombosis has also been reported [111]. Late adverse events reported with OKT3® include infections (especially with cytomegalovirus) and lymphomas.

Anti–Interleukin-2 Monoclonal Antibodies

IL-2 is an important cytokine necessary for the proliferation of cytotoxic T cells. Several mAbs have been developed to target the IL-2 receptor, but currently only one agent is available for clinical use: basiliximab (Simulect®). Daclizumab (Zenapax®) was recently withdrawn from clinical use. Binding of these agents to the IL-2 receptor results in blockade of IL-2–mediated responses. Both are humanized antibodies; with basiliximab, the constant region of the antibody is of human origin; the variable region is of murine origin. Therefore, 75% of the antibody is of human origin.

Because major portions of these agents are of human origin, they tend to have much longer half-lives than does OKT3®. Also, unlike OKT3®, they are not associated with a first-dose reaction. The CD25 component of the IL-2 receptor is primarily focused on naive T cell early activation. Based on this effect, clinical trials in kidney recipients have shown these agents to be effective in preventing acute rejection [112]. It is not indicated for the treatment of established acute rejection episodes, however. For basiliximab, two IV doses of 20 mg (one administered preoperatively and the other on postoperative day 4) are recommended.

Comparable outcomes have been seen in studies comparing basiliximab and polyclonal antibodies and maintenance immunosuppression regimens consisting of CSA, MMF, and steroids [113]. Steroid-free maintenance regimens have also been used in kidney transplantation with anti-CD25 induction [114]. CNI monotherapy or avoidance is not facilitated by the use of anti-CD25 preparations [115]. In all clinical trials to date, basiliximab has been shown to be remarkably safe, with minimal side effects ascribed directly to its use.

Alemtuzumab (Campath-1 H®)

The CD52-specific humanized monoclonal antibody alemtuzumab has the advantages of ease of administration, consistency of monoclonal antibodies, and the benefits of humanization. Alemtuzumab rapidly depletes CD-52 expressing lymphocytes centrally and peripherally resulting from bulk T cell depletion with lesser depletion of B cells and monocytes [116].

Although alemtuzumab depletes all T cell subsets, its action is selective for naive cell types [117]. The T cells that are not depleted exhibit a memory phenotype and are most susceptible to CNI. Maintenance regimens using CNI do best following alemtuzumab induction.

Alemtuzumab facilitates reduced maintenance immunosuppression requirements without an increase in infections or malignant complications in kidney, pancreas, lung, and liver transplantations as compared to historical controls [118–123].

With the increasing use of alemtuzumab as an induction agent, there has been increase in its use as an agent for treating steroid-resistant rejection. There have been anecdotal reports of its use in this setting [124]; additional studies are needed to define its role for this indication.

Rituximab (Humanized Anti-CD-20)

This is a chimeric monoclonal antibody specific for CD20, a cell surface glycoprotein involved in B cell activation and maturation. Rituximab rapidly clears CD20+ cells from the circulation. CD20+ cells are precursors to antibody producing plasma cells, but do not produce antibody themselves; neither do they have a direct effector cell role in rejection. Presence of CD20+ infiltrates has been used as a marker for resistant acute rejection [125]. These cells also have a role in intragraft antigen presentation.

Rituximab has been used as an induction agent in lieu of recipient splenectomy in patients undergoing donor desensitization with plasmapheresis and/or intravenous immunoglobulin [126].

Use of rituximab in high-grade rejection remains investigational. Rituximab has a role in the treatment of Banff 2 and 3 rejection and in reducing antibody formations [127].

The most important indication for the area of rituximab in organ transplantation is as a primary treatment of PTLD—somewhere between immunosuppression withdrawal and the aggressive use of chemotherapy.

FUSION PROTEINS

These are made by the fusion of a single receptor targeting a ligand of interest with a secondary molecule, which is typically the Fc portion of an IgG molecule. Fusion proteins can be composed of humanized components limiting their immune clearance and allowing prolonged administration.

Costimulation-Based Agents

Costimulatory molecules alter the threshold for activation of naive T lymphocytes without having a primary activating or inhibitory function. Fusion proteins have been developed that act by blocking costimulation pathways. The two costimulatory receptors on T cells are CD28 and CD152; these serve

reciprocal roles—CD28 facilitates a T cell response, whereas CD152 reduces it.

The fusion proteins that act by inhibiting costimulation-based pathways, and have been studied in renal transplantation, inhibit CD28 and CD152 signaling and this leads to immunosuppression.

Belatacept (investigative name LEA29Y) is a second-generation costimulation-blockade agent that has two amino acid substitutions that give slower dissociation rate for binding to the ligands of CD28. It prolongs the onset of acute rejection in nonhuman primates and synergizes with basiliximab and other clinically available agents. The BENEFIT study reported the primary outcomes from a randomized, phase III study of belatacept versus CSA in kidney transplant recipients [128]. At 12 months, belatacept regimes demonstrated superior renal function and similar patient/graft survival versus CSA, despite an increase in acute rejection in the early posttransplant period. Belatacept is a promising, nonnephrotoxic option in kidney transplant recipients and is being developed with the aim of providing CNI avoidance [129]. It is intended for use as an induction agent as well as for maintenance immunosuppression.

OTHER IMMUNOSUPPRESSIVE AGENTS

Leflunomide and Malononitrilamide (MNA)

The potential of overimmunosuppression resulting from the long half-life (15 to 18 days) of leflunomide has been partly overcome by the shorter half-life (6 to 45 hours) of one of its synthetic analogues also known as FK778. Leflunomide and its analogues have strong antiproliferative effects on T lymphocytes and B lymphocytes. Inhibition of pyrimidine synthesis by a direct-leflunomide–mediated inhibition of dihydro-orotate dehydrogenase leads to suppression of DNA and RNA synthesis. This group of medications also acts through inhibition of tyrosine kinase. FK778 and leflunomide possess antiviral effects and have been used successfully to treat cytomegalovirus [130] and BK virus nephropathy [131] in renal transplant patients.

FK778, in combination with TAC and corticosteroids, was used in a phase II multicenter study involving 149 renal transplant patients [132]. Patients receiving FK778 experienced fewer acute rejection episodes, but there was no effect on graft survivals at week 16.

Janus Kinase 3 Inhibitors

Janus kinase 3 (JAK3) is essential for the signal transduction from the cytokine receptors of several cytokines to the nucleus. Being expressed only on immune cell makes it an important target for developing new immunosuppressants. Several JAK3 inhibitors are available, but CP-690559 is the most potent and selective JAK3 inhibitors. In vivo effects of CP-690550 include reduction in natural killer cell and T cell numbers, whilst CD8+ effector memory T cells were unchanged [133]. A randomized, pilot study compared CP690550 (15 mg BID [CP15] and 30 mg BID [CP30], $n = 20$ each) with TAC ($n = 21$) in de novo kidney transplant recipients [134]. Patients received an IL2R antagonist, MMF, and steroids. Coadministration of CP-690550 30 mg BID with MMF was associated with overimmunosuppression. At a dose of 15 mg BID, the efficacy/safety profile was comparable to TAC, although there was higher rate of viral infection. Although, further dose ranging evaluation of CP-690550 is needed, it may become an important component of CNI avoidance regimens.

IMMUNOSUPPRESSIVE STRATEGIES

Immunosuppressive strategies must take into account the risk of an acute rejection episode, the consequences of an acute rejection episode, the side effects of the immunosuppressive agents, and the consequences of graft loss. The relative importance of each factor may vary depending on the organ transplanted. For example, for kidney recipients, an acute rejection episode is a major risk factor for chronic rejection; strategies must minimize the incidence of acute rejection. For liver recipients, an acute rejection episode usually is easily reversed and has little long-term significance; therefore, lower initial doses of immunosuppression can be used and then increased in those patients who suffer a rejection episode. Dialysis provides a backup if a kidney graft fails, whereas there is no recourse (other than a retransplant) for failure of many other solid-organ grafts. Therefore, particularly for heart and lung recipients, early aggressive immunosuppressive strategies are warranted.

Thus, no single approach applies uniformly across all organs to posttransplant immunosuppressive therapy. Immunosuppressive agents can be categorized according to their use:

Induction—those used for a limited interval at the time of transplant;

Maintenance—those used long term for maintenance of immunosuppression; and

Antirejection—those used for a short time or in high doses to reverse an acute rejection episode.

Considerable overlap exists among these categories, however. For example, the monoclonal and polyclonal antibodies can be used for induction or rejection treatment; PRED is used in high doses for induction or antirejection therapy but in low doses for maintenance therapy; and, in some situations, the doses of maintenance therapy drugs (e.g., TAC) are increased to treat rejection.

Finally, many transplant programs individualize immunosuppression depending on the perceived immunologic risk of rejection and graft loss for that recipient. For example, for kidney recipients, immunosuppressive protocols at a single center may vary for human leukocyte antigen–identical living donor recipients, nonidentical living donor recipients, low-risk cadaver donor recipients, and high-risk (e.g., blacks, those with a high panel-reactive antibody or delayed graft function, retransplant) recipients.

Induction

All recipients (except for identical-twin kidney recipients) require immunosuppressive therapy at the time of transplant. Many transplant centers begin with the same immunosuppression that is used for long-term maintenance. Other centers begin using induction therapy with polyclonal (e.g., Thymoglobulin, ATGAM) or monoclonal (e.g., basiliximab, OKT3, alemtuzumab) antibodies. The goal of induction immunosuppression is to provide powerful immunosuppression peritransplant, decrease the overall incidence of rejection, and permit delay in introducing other maintenance agents such as the CNI.

Prospective randomized studies have shown a decreased incidence of acute rejection episodes with early posttransplant induction therapy. The drugs are expensive, however, and a

TABLE 181.2

DRUGS (MONOTHERAPY OR COMBINATION) CURRENTLY USED FOR LONG-TERM MAINTENANCE THERAPY

CSA monotherapy	FK monotherapy
CSA-P	FK-P
CSA-P-MMF	FK-P-MMF
CSA-P-RAPA	FK-P-RAPA
CSA-MMF	FK-MMF
CSA-RAPA	FK-RAPA
CSA-P-AZA	FK-P-AZA
CSA-AZA	FK-AZA
MMF-P	MMF-RAPA
RAPA-P	
RAPA-MMF-P	

AZA, azathioprine; CSA, cyclosporine; FK, tacrolimus; MMF, mycophenolate mofetil; P, prednisone; RAPA, sirolimus.

TABLE 181.3

ADVANCES IN IMMUNOSUPPRESSION OF SOLID-ORGAN TRANSPLANTATION

1. Major emphasis has been in the area of reduction of toxicities of immunosuppressive agents/combinations.
2. With the increasing use of tacrolimus, steroid-free protocols have been used successfully.
3. Use of depletional antibodies like alemtuzumab has allowed the successful use of tacrolimus monotherapy.
4. To circumvent nephrotoxicity of CNIs, several nonnephrotoxic agents like sirolimus, mycophenolate, belatacept, and JAK3 inhibitors have been developed. Use of IL-2 receptor blockers as induction therapy along with combination of nonnephrotoxic agents might one day lead to successful CNI-free immunosuppression.
5. Use of rituximab in the treatment of B-cell (CD20+)–mediated rejection.

CNIs, calcineurin inhibitors.

long-term benefit has not been well documented for low-risk recipients. As a consequence, some centers use induction for all recipients, other centers use it for no recipients, and still others individualize depending on rough calculations of immunologic risk. More recently, the advantages of steroid- or calcineurin-sparing protocols have been touted, so many centers use short-term induction with IV antibodies in an attempt to lower the doses of other immunosuppressive drugs.

One perceived advantage of antibody induction is the ability to use lower doses of CNIs early posttransplant. A frequent concern is perioperative renal function (of the kidney graft for kidney recipients; of the native kidneys for liver, heart, or lung recipients). Because CNIs are nephrotoxic, delaying their introduction until renal function has recovered may be beneficial.

Maintenance Therapy

First Six Months

With the introduction of multiple new agents in the 1990s, immunosuppressive protocols have become more varied. Table 181.2 illustrates the many combinations currently used for long-term posttransplant maintenance therapy. At most centers, CINs (CSA or TAC) form the basis of immunosuppressive protocols. These drugs have been used as monotherapy and/or in combination with PRED or an antimetabolite. Prospective randomized trials have shown a lower incidence of acute rejection when MMF replaces AZA in these combination protocols [54–56]. Similar trials have shown a lower incidence of acute rejection in SRL versus AZA-treated recipients [83]. Additional studies are needed to determine the relative benefits and risks of MMF versus SRL.

Of interest, CNI-free protocols have been devised. The major goal of such protocols is to avoid the nephrotoxicity associated with use of CNIs. The combination of SRL and MMF has been used to achieve these results. Although nephrotoxicity can be avoided, relatively high doses of both drugs need to be used; as discussed previously, they each have their own side effects. In other randomized trials of CNI-free protocols, belatacept [128] and JAK3 inhibitors [133] have been used.

Considerable debate exists as to whether CNI should be used as monotherapy or combined as double or triple therapy for early posttransplant immunosuppression. Preconditioning with alemtuzumab (Campath 1-H) followed by TAC monotherapy has been successfully used in kidney transplantation with low acute rejection rates [121]. It is important to note that for all protocols, monitoring drug levels and maintaining CNI levels within a specified drug range seem critical to prevent acute rejection episodes early posttransplant.

Late Posttransplant

It is unclear whether all agents used for maintenance therapy in the early posttransplant period need to be continued late posttransplant. Meta-analyses have shown no risk to stopping AZA or CNI late posttransplant [135,136]. Meta-analyses of studies of PRED withdrawal in kidney recipients have shown an increased risk of rejection, however, and an increased risk of graft failure in recipients who stopped PRED [136,137]. In addition, single-center studies have shown no impact of stopping MMF in the late posttransplant period.

CONCLUSIONS

Since 1992, following the introduction of a number of new immunosuppressive agents, short-term graft and patient outcomes have improved considerably. However, the side effect of immunosuppressive agents continues to present a major problem. With the increasing use of TAC, steroid-free protocols were used successfully. Development of depleting monoclonal antibodies like alemtuzumab has led to the use of TAC monotherapy as maintenance immunosuppression. In kidney transplantation, long-term outcomes have been affected by the nephrotoxicity of CNI. In nonrenal transplant recipients, CNI toxicity has led to renal insufficiency and failure in a significant number of instances. Development of nonnephrotoxic agents like SRL, MMF, belatacept, and JAK3 inhibitors and their use in combination will some day lead to the successful use of CNI-free immunosuppression. A summary of some of the advances in the field of immunosuppression is shown in Table 181.3.

Another major advantage of the availability of several immunosuppressive agents is that immunosuppression can now be tailored for the individual patient. Those having drug-specific toxicity can be switched to another drug with similar efficacy but differing side effects.

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CHAPTER 182 ■ CRITICAL CARE PROBLEMS IN KIDNEY TRANSPLANT RECIPIENTS

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INTRODUCTION

A kidney transplant (KTx) remains the most definitive and durable solution for patients reaching end-stage renal disease (ESRD). A successful transplant, as compared with dialysis, can provide a higher quality of life for a longer period at an overall lower cost for the more than 104,000 patients currently awaiting a KTx on the United Network for Organ Sharing waiting list [1,2]. In 2006, in United States KTx centers, the cumulative 1-year graft survival rate was 91.3% for deceased donor recipients and 96.4% for living donor recipients; an analysis of recipients transplanted in 2002 revealed a 5-year graft survival rate of 68.9% for deceased donor recipients and 81.5% for living donor recipients. The half-life graft survival time now projected for deceased donor recipients is approximately 10 years; for living related donor recipients, almost 18 years, depending on the human leukocyte antigen (HLA) match [3–5]. Despite these encouraging results, the waiting list continues to expand, and the living and deceased donor pools have fallen further behind; this divergence results in recipients who can be subjected to the ill effects of uremia and dialysis for more than 5 years pretransplant. Critical care providers therefore face a cohort of patients with a higher acuity of illness than seen even a decade ago. This chapter discusses the salient points of critical care that KTx recipients must receive to optimize their outcomes.

PRETRANSPLANT EVALUATION

Thoughtful patient selection and a thorough pretransplant evaluation of transplant candidates are essential for optimal transplant outcomes; because hypertension, diabetes mellitus, and cardiovascular disease are ubiquitous in this group, risk stratifying is helpful. The pretransplant evaluation should be exhaustive (covering gastrointestinal, pulmonary, neurologic, genitourinary, and infectious disease concerns). The cardiovascular examination is the most important and possibly the most unreliable. Candidates at increased risk for coronary artery disease or cardiac dysfunction, especially those with diabetes, should undergo noninvasive cardiac stress testing. For those with reversible cardiac ischemia, coronary angiography is mandatory to elucidate the need for percutaneous coronary artery balloon dilation or even coronary artery bypass.

The problem lies in the most troublesome deficiency in noninvasive testing—that is, the suboptimal sensitivity for cardiac death and infarction. In a meta-analysis, the sensitivity of the pretransplant cardiac perfusion study for myocardial infarction was only 0.7; for cardiac death, only 0.8 [6,7]. Therefore, the onus remains on transplant physicians to have a high suspicion for life-threatening cardiovascular disease in this patient population; even uremic young adults (< 40 years old) should be heavily scrutinized, because more than 90% of them who

had renal insufficiency during childhood will have significant cardiac or carotid disease.

Even with an aggressive approach to pretransplant evaluation, cardiac complications occur in 6% of recipients during the first-month posttransplant [6]. Candidates with a history of stroke or transient ischemic attacks (TIAs) require a carotid duplex ultrasound to exclude critical carotid stenoses. Pulmonary function testing should be assessed in candidates with a history of pulmonary disease such as emphysema or asthma. Also, at least one group reported an abnormally high prevalence of pulmonary hypertension (40%) in recipients who were undergoing hemodialysis (HD) via an arteriovenous fistula [8].

Up to 10% of the HD population has antihepatitis C antibodies; therefore, all KTx candidates should be screened, and abnormal liver function test results should stimulate a more thorough evaluation [9]. Cholecystectomy should be considered for candidates with symptomatic cholelithiasis.

Gastrointestinal disease, ranging from gastritis and peptic ulcer disease to colonic diverticulosis, is more common in patients with ESRD. Liberal use of bidirectional endoscopy is justified in this population, and colonoscopy is mandatory in all candidates 50 years and older. Recurrent urinary tract infections or a history of bladder dysfunction mandates a urologic evaluation.

Candidates with a personal or family history of hypercoagulability should undergo a thrombophilia evaluation. If appropriate pretransplant evaluations are readily performed, therapeutic measures can begin in a timely manner to avoid many potential complications (some life threatening).

PERIOPERATIVE CARE

Pretransplant Preparation

Proper pretransplant preparation in the days before the operation is essential for optimal graft and recipient outcome. Ideally, HD-dependent patients can undergo their routine HD session the day before their KTx; appropriate electrolyte panels should be checked within hours of anesthesia induction. Dialysis catheter sites require examination for infection; for recipients on peritoneal dialysis, culture and Gram stains of their peritoneal fluid should be obtained. Each recipient should undergo a repeat history and physical examination, electrocardiogram (ECG), chest x-ray (CXR), and laboratory examination within days before their transplant, to detect any interim health derangements since their last physician visit. A medication list review is mandatory to confirm the cessation of some drugs (e.g., warfarin) and the continuation of others (e.g., beta-blockers), which may affect intraoperative and postoperative outcomes. Bowel preparation occurs at some centers the evening before the operation.

Intraoperative Care

The type of invasive monitoring during the KTx should reflect the nature and degree of the individual recipient's comorbidities. A central venous catheter is often introduced to facilitate monitoring of central venous pressure (CVP), thereby helping to guide intraoperative and postoperative fluid management (particularly in high-risk recipients). Continuous arterial blood pressure monitoring is considered mandatory at most centers, given the high prevalence of hypertension in this population as well as the importance of optimizing the blood pressure at the time of reperfusion. The indications for pulmonary artery pressure monitoring are more controversial, but it may be justifiable for those with significant cardiac dysfunction (e.g., ejection fraction < 30%), valvular abnormalities, or known pulmonary artery hypertension. A 20-Fr 3-way Foley catheter is placed in the bladder, which is then filled with saline and antibiotic solution. Compression stockings and sequential compression devices provide deep venous thrombosis prophylaxis.

Communication between the anesthesia and surgical teams is paramount during the KTx. Adequate intravascular volume, especially at the time of reperfusion, is critical to allow the graft to function immediately. The importance of immediate graft function, with avoidance of acute tubular necrosis (ATN) and of delayed graft function (DGF), cannot be overstated: both ATN and DGF have been found to be predictive of increased patient mortality [10]. CVP should be in the range of 10 to 15 mm Hg. Systolic blood pressure, ideally, should be greater than 120 mm Hg at the time of graft reperfusion. Vasopressors (except for low-dose dopamine) should be avoided in lieu of volume expansion. Mannitol at 1 g per kg, when combined with optimal volume expansion, has been shown to decrease the incidence of ATN; it is given concurrently with furosemide at many centers [11]. After the ureteral anastomosis is completed, urine output is measured frequently, which helps guide volume resuscitation in the immediate postoperative period.

Immediate Postoperative Care

Recipients with a higher acuity of illness may require admission to the intensive care unit (ICU) for optimal monitoring; however, the vast majority can receive appropriate care on a solid-organ transplant ward. Serial complete blood counts, coagulation profiles, and chemistries should be obtained; myocardial ischemia should be excluded with serial troponin measurements in the appropriate subgroup of recipients with cardiac risk factors. CXR and ECG are obtained in the immediate postoperative period. Electrolyte abnormalities (hyperkalemia, hypokalemia, hypomagnesemia, and hypocalcemia) are common and should be corrected.

For recipients with initial graft function, fluid management consists of equivalent replacement of urine output, which is measured hourly; if cardiac dysfunction is not present, urine output can initially be replaced milliliter for milliliter. For recipients with high-output diuresis (≥ 500 mL per hour), 1% dextrose with 0.45% normal saline solution should be administered; potassium replacement may also be necessary, but should not exceed 0.3 mEq per kg per hour intravenously; serum potassium levels should be serially monitored. For recipients with cardiac dysfunction and high-output diuresis (≥ 500 mL per hour), the volume of fluid replacement should be lower than urine output (i.e., 0.5 mL of replacement for 1 mL of urine). In general, within 24 hours posttransplant, urine output in recipients with initial high-output diuresis is frequently appropriate for the recipient's weight and kidney function; fluid replacement is then converted to a continuous rate of 100 to 150 mL per hour. If initial urine output is less than 500 mL per hour, fluid replacement in nondiabetic recipients should consist of 5% dextrose with 0.45% normal saline solution. In diabetic recipients, 0.45% normal saline solution should be used.

Most KTx recipients are cared for on a surgical ward dedicated to solid-organ transplantation. ICU monitoring may become necessary if complications develop, at any time and at any stage posttransplant. The higher susceptibility of transplant recipients to complications is related to their comorbidities, immunosuppression intensity and duration, and immediacy of graft function. Thus, deceased donor recipients, with their accompanying higher DGF rate and increased immunosuppressant load, are more prone to complications than are living related donor recipients. Deceased donor recipients are also more likely to have felt the effects of prolonged uremia and dialysis, as compared with living donor recipients.

Many risk factors directly correlate with the incidence and severity of posttransplant complications. Between 15% and 30% of high-risk transplant recipients require specific critical care.

CRITICAL EVALUATION OF DYSFUNCTIONAL GRAFTS

Early graft function is affected by numerous factors, such as the quality of the donor (i.e., living vs. deceased), cold and warm ischemia times, and the recipient's volume status and medical stability. Urine output is the most readily apparent parameter to gauge graft function in the initial hours posttransplant, but it may be influenced by a residual effect of diuretics infused during the operation or of urine produced by the recipient's native kidneys. A consistent, downward trend in the serum creatinine level and brisk diuresis (> 100 to 200 mL per hour) confirm that the graft is functioning well.

Monitoring the function of an initially delayed or slow functioning graft is more difficult, because urine output is minimal, and the creatinine level may remain at baseline. Doppler ultrasound plays a vital role in surveillance of the newly transplanted kidney and is the most helpful modality in evaluating a dysfunctional graft. Intensivists must be aware of the medical and surgical complications that can occur in the early posttransplant period and that can result in an abrupt change in graft function; graft salvage is only possible with an efficient, expeditious evaluation leading to rapid therapeutic maneuvers.

Medical Complications Leading to Early Graft Dysfunction

Acute Tubular Necrosis

ATN is the most common cause of impaired kidney function immediately posttransplant. Although ATN is rare in living related donor recipients, its incidence averages 35% in deceased donor recipients. It may occur immediately after revascularization or, in grafts with initial diuresis, have a more delayed presentation; dysfunction may last from several days to several weeks. In deceased donor grafts, ATN is usually secondary to prolonged ischemia times, but may also occur in recipients with negative immunologic factors, for example, a high panel-reactive antibody percentage directed against HLAs, a retransplant, and a poor HLA match between donor and recipient. Donor factors such as age, underlying disease (e.g., hypertension), and use of vasopressors (during both procurement and the transplant operation) also contribute to ATN. As stated before, ATN has a detrimental effect not only on later graft function, but also on overall graft survival and postoperative morbidity [12].

Recipients with ATN have a higher incidence of acute rejection, which ultimately lowers graft survival rates by subjecting the kidney to higher rates, and more aggressive progression, of chronic allograft nephropathy [13]. ATN must be differentiated from a vascular catastrophe (renal artery or vein thrombosis) and early acute rejection. Thrombosis should be excluded within 24 hours posttransplant with a Doppler ultrasound to confirm vascular patency. For recipients with ATN, HD frequently must be reinstituted; after a few days to several weeks, kidney function recovers in more than 95% of recipients.

Acute Rejection

A complete discussion of acute kidney graft rejection is beyond the scope of this chapter, however, *acute antibody-mediated rejection* may lead to a rapid decline in early graft function and is therefore relevant. Alloantibodies may form in recipients with a history of blood transfusions, pregnancies, or previous organ transplants; these antibodies can be detected by cross-matching pretransplant, which may, in fact, preclude the transplant. Fortunately, desensitization protocols are in place at many centers that may allow highly sensitized KTx candidates to proceed with a transplant. They do, however, remain at much higher risk for rejection; when these preformed antibodies target capillary endothelium, the complement system may be activated, ultimately resulting in a rapid deterioration of graft function. Only a kidney graft biopsy can confirm the diagnosis; performing the biopsy via an open approach minimizes potential bleeding complications [14,15].

Recurrence of Kidney Disease

Most acute kidney diseases rarely recur, but *focal segmental glomerulosclerosis* (FSGS) and *hemolytic uremic syndrome* (HUS) deserve special mention for their ability to cause profound, early graft dysfunction. Posttransplant nephrotic range proteinuria (i.e., > 3.5 g per day) in a recipient with known FSGS should prompt an immediate biopsy, which will likely show diffuse foot process effacement [16]. When graft dysfunction is accompanied by signs of microvascular trauma (i.e., low haptoglobin levels, elevated lactate dehydrogenase levels, and the presence of schistocytes on blood smears), HUS should be suspected. It may be recurrent or de novo: calcineurin inhibitors (CNIs) (i.e., tacrolimus, cyclosporine) have been long implicated as a causative agent [17].

Surgical Complications Leading to Early Graft Dysfunction

Hemorrhage from the venous or arterial anastomosis is rare. Most postoperative bleeding emanates from small vascular tributaries in the renal hilum or from diffuse hemorrhage in the retroperitoneal dissection field. In the confined retroperitoneal space, bleeding usually tamponades, so reexploration is seldom required. Subcapsular bleeding, albeit less common, is considerably more morbid and can lead to significant and irreversible kidney damage if not quickly recognized and controlled. Bleeding should be suspected if recipients are tachycardic, hypotensive, or oliguric, or if they require several units of blood in the early posttransplant period.

Although the incidence of *vascular thrombosis* is low (0.7% to 5%), it almost invariably results in graft loss [18]. Any sudden change in urine output or creatinine levels in the first several weeks posttransplant should prompt urgent Doppler sonography. The best opportunity for graft salvage occurs if the thrombosis is discovered while the patient is in the recovery room; after several hours, salvage is unlikely and nephrectomy is usually necessary.

Causative factors for *renal artery thrombosis* include unidentified intimal flaps, perfusion or preimplantation arterial or graft damage, size discrepancy between donor and recipient vessels, hypotension or hypoperfusion (especially in pediatric recipients with adult donors), and technical difficulties in kidneys with multiple arteries [18]. Other arterial complications include aneurysms and stenosis. Aneurysms may be anastomotic (pseudoaneurysm) or infected (mycotic). Magnetic resonance angiography can usually confirm the diagnosis without exposing the kidney to nephrotoxic contrast; conventional angiography is reserved for equivocal cases. Aneurysms require surgical repair, which can result in graft loss. For recipients with iliac or renal artery stenosis, percutaneous balloon dilation is the treatment of choice; if unsuccessful, surgical repair is necessary.

Renal vein thrombosis, a complication in 0.3% to 4.2% of KTx recipients, may be caused by kinking of the anastomosis, intimal injury during organ procurement, pressure on the vein

secondary to a fluid collection (i.e., lymphocele, urinoma, or hematoma), compartment syndrome, and extension of an iliofemoral thrombosis [19]. Renal vein thrombosis usually occurs within the first few posttransplant days and may be characterized by sudden onset of pain and graft swelling, hematuria, and, in the case of iliofemoral thrombosis, an edematous leg. The diagnosis is confirmed by Doppler ultrasound, which will show a pulsatile renal artery (with reversal of blood flow) running into the hilum of an enlarged kidney, possibly surrounded by hematoma. If thrombosis is complete, nephrectomy is necessary, although recovery of function after surgical embolectomy or thrombolytic therapy has been report. If thrombosis is incomplete, immediate thrombectomy is recommended (or, as an alternative, urokinase, and heparin treatment).

Urologic complications are rarely life threatening, but can add significant morbidity and can lead to inferior graft survival rates if not handled in a systematic manner. The incidence of urologic complications ranges from 5% to 14% in most KTx series [20].

Hematuria from the distal ureter or the cystostomy suture line generally ceases within the first 12 to 24 hours posttransplant, but it may result in clot formation in the bladder, especially in grafts with poor initial diuresis. Bladder clots or debris may lead to obstructive uropathy, which presents with a sudden cessation of urine output; obstructive uropathy is the most common cause of new-onset anuria in the immediate postoperative period and should be readily remedied with catheter irrigation. If anuria persists, emergent Doppler ultrasound will (1) confirm renal artery and vein patency and (2) rule out a large retroperitoneal hematoma causing hydronephrosis or a retroperitoneal compartment syndrome. Persistent hematuria due to a bleeding diathesis or technical error in the ureteroneocystostomy may lead to the formation of large bladder clots, which may present with suprapubic pain and "bladder spasms" or with frequent Foley catheter occlusions; if continuous bladder irrigations do not restore diuresis, manual hematoma evacuation is performed via a 20-Fr 6-eye Foley catheter. If hematuria is caused by a posttransplant biopsy, with subsequent clot formation in the renal pelvis, temporary percutaneous placement of a nephrostomy tube may be necessary. Most hematuria-related complications require close urine output monitoring, but rarely ICU admission.

Urine leaks most commonly occur at the ureteroneocystostomy anastomosis and can present in the first few postoperative days (technical error) or during the first several weeks (ureteral necrosis). Symptoms and signs of a urine leak may include graft swelling and tenderness, fever, wound drainage, oliguria, scrotal or labial edema, and ipsilateral thigh swelling. Diagnostic studies that confirm the diagnosis include nephroscintigraphy, retrograde cystography, or pelvic computed tomography (CT) scans. Perirenal fluid collections can be aspirated and sent for fluid creatinine level testing to confirm the diagnosis. Minor urine leaks may spontaneously resolve after several weeks with Foley catheter decompression. Recipients with significant leaks in the early postoperative period are best served by immediate exploration and reimplantation of the ureter. Other investigators advocate for an initial percutaneous maneuvers, namely, a percutaneous nephrostomy and stent placement for 4 to 8 weeks; success rates up to 90% have been reported in some centers with this approach [21,22].

Ureteral stenosis becomes evident months posttransplant and may be secondary to rejection, ischemia, infection, or a tight ureteroneocystostomy. Recipients usually have an elevated creatinine level and hydronephrosis (visualized on ultrasound). A percutaneous nephrostomy elucidates the location and degree of the stenosis and is typically followed by a balloon dilatation with a temporary stent tube. If balloon ureteroplasty and stenting fail, operative repair is required (but fortunately only in the vast minority of recipients). A localized distal ureteral stenosis can be repaired by reimplanting the transplanted ureter, but most stenoses require a ureteroureterostomy (to the native ureter) or an ureteropyelostomy (native ureter to the graft's renal pelvis) because of extensive adhesions and lack of graft mobility [22].

Lymphoceles or hematomas can cause compression of the iliac veins (leading to leg edema or deep venous thrombosis) as well as compression of the ureter (leading to hydronephrosis and impaired graft function). Lymphoceles are a collection of lymph in the retroperitoneal space secondary to disruption of lymphatic vessels along the external iliac artery. The incidence can be decreased with careful ligation of the lymphatic vessels during dissection of the iliac vessels. Symptomatic lymphoceles can be diagnosed by ultrasound and treated with percutaneous drainage. Recurrent lymphoceles are approached laparoscopically [23] or, less commonly, by open laparotomy, to create a peritoneal window for decompression of the lymph leak.

NON-RENAL POST-TRANSPLANT COMPLICATIONS

Cardiovascular Complications

The incidence of *cardiac complications*, the most common cause of death posttransplant [24], depends on the extent of underlying cardiac disease, on the efficacy of the preoperative cardiac evaluation, and on the function of the newly transplanted kidney. Correction of uremia by immediate posttransplant graft function improves the cardiac index, stroke volume, and ejection fraction [25]. In contrast, recipients with ATN experience persistent uremia and oliguria, which may lead to perioperative fluid overload and congestive heart failure if immediate HD is not performed to correct fluid retention and electrolyte derangements. Recipients with diabetes, hypertension, and significant coronary disease are more likely to develop cardiac complications if there is no urine output immediately posttransplant; therefore, such recipients require perioperative ICU monitoring, especially if their left ventricular function is poor (e.g., ejection fraction < 30%). Pulmonary artery catheter (PAC) placement to optimize hemodynamics might be prudent, especially in diabetic recipients with coronary artery disease.

Myocardial infarction is uncommon in the perioperative period. It is mostly seen in diabetic recipients with preexisting coronary artery disease who have complicated posttransplant courses with resultant hypotension. ICU admission, serial troponin evaluations, and close monitoring of their hemodynamic parameters are mandatory, especially when complicated by postoperative ATN. Although uncommon in the early posttransplant period, myocardial infarction is one of the major causes of death long-term in transplant recipients. In diabetic recipients, the duration of their diabetes and the presence of preexisting coronary artery disease have an impact on the incidence and severity of posttransplant myocardial infarction, which is the main cause of death in this subgroup. Data suggest that maintaining the hematocrit above 30% is prudent in diabetic recipients: doing so is associated with a 24% decrease in cardiac morbidity in the initial 6 months posttransplant [26].

The incidence of *pericarditis* in the early posttransplant period is 1% to 3% [27]. It has been attributed to infections (e.g., cytomegalovirus [CMV]), fluid overload, and certain medications (e.g., minoxidil). The main factor, however, is uremia. Most episodes of viral or uremic pericarditis occur during the first 8 weeks posttransplant. In contrast, the less frequent bacterial pericarditis develops later, often in recipients with advanced septic complications. Bacterial pericarditis usually requires, besides antibiotic treatment, surgical or ultrasound/CT–guided drainage. Pericardiocentesis is mandatory if cardiac failure, hypotension, or cardiac tamponade develops. Recipients with clinical symptoms of pericarditis require ICU monitoring.

Although *hypertension* is the most common long-term complication posttransplant, with an incidence of up to 50%, it may also require aggressive management immediately posttransplant. Overzealous perioperative hydration may lead to postoperative exacerbation of baseline hypertension. Abrupt cessation of antihypertensive medications should be avoided as well; however, most clinicians do advocate removal of angiotensin-converting enzyme (ACE) inhibitors from the perioperative regimen. CNIs, a part of virtually every immunosuppressive regimen, may also lead to hypertension, especially when they reach toxic levels. The pathophysiology of CNI-induced hypertension has not been fully elucidated, but appears to be multifactorial. CNIs directly lead to systemic vascular constriction by reducing prostacyclin and nitric oxide production while increasing serum levels of endothelin-1; this imbalance favors widespread constriction. Afferent arteriole vasoconstriction in the kidney leads to diminished glomerular filtration, which enhances sodium retention and exacerbates hypertension. Calcium-channel blockers appear to be superior at obviating the renal vasoconstriction induced by CNIs [28–30].

More intensive blood pressure monitoring is warranted in recipients with systolic blood pressure greater than 180 mm Hg or diastolic pressure greater than 100 mm Hg. Treatment often is simply to restart their home regimen, which is typically a combination of calcium-channel blockers, vasodilators, and diuretics. Unless a strong contraindication is noted, perioperative β-blockade is mandatory in this high-risk cohort of surgical patients in order to minimize perioperative cardiac events [31]. Consensus has not been reached on the optimal antihypertensive regimen, given that many drugs interfere with kidney function and CNI metabolism; treatment is based on each individual's response. ICU monitoring and intravenous (IV) antihypertensive infusions (e.g., titration with sodium nitroprusside) may be required, but early posttransplant hypertension can usually be controlled with appropriate oral antihypertensive medications [32].

Hypotension, either intraoperatively or immediately posttransplant, is the single most detrimental nonimmunologic event associated with an increased incidence of graft loss or severe dysfunction. Intraoperative hypotension is usually related to volume depletion or anesthetic agents. Intravascular volume status is assessed most accurately via CVP monitoring, before unclamping, to avoid poor graft perfusion. Posttransplant hypovolemia, especially in recipients with immediate graft function, is often caused by inadequate fluid replacement and should be treated accordingly. Cardiac dysfunction and bleeding must be excluded in recipients with early posttransplant hypotension. Induction immunosuppression (e.g., Thymoglobulin) may lead to hypotension, which is readily reversed by slowing the infusion rate.

As compared with the general population, uremic recipients are more prone to *deep venous thrombosis* (DVT) posttransplant. The incidence of DVT ranges from 1% to 4%. DVT has been linked both to high-dose corticosteroid therapy early posttransplant and to "rebound" hypercoagulability, which is attributed to overcorrection of impaired platelet aggregation and thrombin generation (both associated with uremia). Thrombophilic events of concern within the first few weeks posttransplant include decreased fibrinolytic activity and an increase in plasminogen activation inhibitors. Other risk factors for the development of DVT are postoperative immobilization, increased blood viscosity from posttransplant erythrocytosis, cyclosporine use, and posttransplant hematoma and lymphocele formation (both of which diminish the venous return from the leg and may result in stasis and ultimately thrombosis).

In contrast, neither transient marked elevation nor moderate sustained elevation of hemoglobin levels per se seem to be directly associated with an increased incidence of thromboembolic complications; DVT rarely occurs during periods of peak hemoglobin elevation. Elevated hemoglobin levels (in combination with increased whole blood viscosity, iron deficiency, or hypertension), as well as older recipient age and diabetes, contribute to the occurrence of thrombotic events posttransplant. Aggressive therapeutic phlebotomy to maintain the hematocrit level at less than 55% has been recommended in such recipients. The diagnosis is made clinically and confirmed by Doppler ultrasound to assess the extent of DVT and the potential involvement of the kidney graft in the thrombotic event. Because the kidney is a "high-flow" organ, DVT usually stops at the level of, or distal to, the renal vein anastomosis. About two-thirds of the time, DVT occurs on the graft side.

Once the diagnosis of DVT has been established, standard therapy is systemic heparinization followed by warfarin administration for 3 to 6 months. If DVT occurs in the immediate postoperative period, when heparinization can cause major bleeding, an inferior vena cava filter is an appropriate alternative. Surgical intervention is indicated only if phlegmasia cerulea dolens develops. Venous thrombectomy (with or without creation of a temporary arteriovenous fistula) and, if necessary, fasciotomy are the treatments of choice in that rare situation [33–35].

Pulmonary embolism is rare (< 1%) after a KTx, yet more common than in the uremic nontransplant population. In kidney recipients, especially those who were uremic pretransplant, the coagulation system is activated and enhanced during the first-week posttransplant, which may explain the overall higher incidence of pulmonary embolism. In general, quick recovery posttransplant lowers the rate of pulmonary embolism. Pulmonary embolism as a result of DVT occurs in fewer than 1% of kidney recipients, but, if it does occur, the mortality rate is about 40%.

Pulmonary Complications

Most KTx recipients do not require ventilator support postoperatively, but prolonged support may be indicated in case of pulmonary dysfunction secondary to intraoperative fluid overload, cardiac dysfunction, or underlying lung disease.

Pulmonary edema usually is the result of overresuscitation intraoperatively and is more likely to occur in recipients who underwent inadequate pretransplant HD and/or overzealous volume infusion accompanied by a poorly functioning graft. As discussed previously, poor early graft function requires much more precise fluid management to optimize volume status for the graft, without placing the recipient at unacceptable risk for cardiopulmonary complications. Chest radiography in the recovery room to assess pulmonary status should be routine, particularly when anti-CD3 murine monoclonal antibody (OKT3) is given intraoperatively; fluid-overloaded recipients can respond to their first dose of OKT3 with flash pulmonary edema [36,37]. Fortunately, few modern immunosuppressive regimens include OKT3 for induction; its primary role is to combat acute rejection. Recurrent pulmonary edema may be an atypical manifestation of a kidney graft renal artery stenosis.

Pulmonary hypertension (PHT), a known risk factor for death in liver transplant recipients, has now been found to be an independent risk factor for inferior rates of patient survival after a KTx. KTx recipients with known PHT may require ICU care postoperatively, often guided by PAC monitoring [38].

Acute respiratory distress syndrome (ARDS) affects 0.2% of all KTx recipients. It is more likely in recipients with poor initial graft function and in those receiving antithymocyte globulin for induction of immunosuppression. Not surprisingly in this population with a higher acuity of illness, the mortality rate of KTx recipients with ARDS is prohibitive at well over 50% [39].

Metabolic Complications

Hyperkalemia is a frequent perioperative derangement, making serial serum potassium determinations necessary. Surgical trauma and transfusion of banked blood might cause intraoperative hyperkalemia, which can be corrected with intravenous glucose and insulin, thereby driving extracellular potassium into the cells. Posttransplant, hyperkalemia can develop immediately in recipients with ATN and later in those with poor graft function due to severe acute or chronic rejection. Hyperkalemia is frequently secondary to physiologic abnormalities or to medications that decrease potassium excretion in the urine. Such abnormalities include a decrease in the glomerular filtration rate (GFR), injury to distal tubules (which are a major site of potassium secretion in the nephron), and a decrease in plasma aldosterone levels. CNIs cause vasoconstriction of the afferent arterioles and direct damage to distal tubules, leading to hyperkalemia and decreased GFR. Medications that decrease potassium excretion include trimethoprim–sulfamethoxazole (TMP–SMX) (which blocks sodium and potassium exchange in distal tubules), ACE inhibitors, angiotensin-2 receptor-antagonists, and nonsteroidal anti-inflammatory agents (which suppress plasma aldosterone levels leading to higher potassium levels). Hyperkalemia can also be a drug-related side effect (e.g., impeded intracellular potassium entry by a beta-blocker). Therapeutically, a potassium-binding ion exchange resin (e.g., Kayexalate®) can be given or, if a rapid decrease of serum potassium is required, IV glucose, insulin, and bicarbonate infusions. Recipients with hyperkalemia due to poor graft function eventually require HD.

Copious diuresis (> 500 mL per hour) immediately posttransplant may result in *hypokalemia,* which requires appropriate potassium replacement. Recipients requiring more than 0.3 mEq per kg per h should be placed on a cardiac monitor.

Less frequently, *hypomagnesemia* and *hypophosphatemia* occur in recipients with high-output diuresis initially. Hypomagnesemia is secondary to drug-related renal wasting (e.g., cyclosporine, tacrolimus, diuretics, aminoglycosides, and amphotericin B), poor dietary intake, and malabsorption from the gastrointestinal tract. Hypophosphatemia is secondary to renal wasting of phosphate, caused by secondary hyperparathyroidism, glucocorticoids (which inhibit the tubular reabsorption of phosphate), and antacids (which bind phosphate in the gastrointestinal tract).

Infectious Complications

A comprehensive review of the role of infectious diseases after a KTx is beyond the scope of this chapter, except for infections known to develop in the immediate posttransplant period (e.g., 1 to 4 weeks). Infections do not occur at random, but rather according to a timetable. Bacterial infections caused by nosocomial pathogens or recipient colonizers tend to occur early posttransplant, affecting the anatomic sites breached during the transplant operation itself, namely, the lungs, blood (indwelling vascular catheters), superficial wounds, and perinephric (deep) space [40].

As compared with all other solid-organ transplant recipients, KTx recipients have the lowest incidence of *pneumonia*; still, it develops in about 16% of KTx recipients and carries with it a mortality rate of 10% to 13%. In the first posttransplant month, 90% of the pneumonic processes are bacterial, particularly staphylococcal and nosocomial Gram-negative species; fungal infections (i.e., *Candida, Aspergillus*) are more frequent when the recipient is on a more intensive immunosuppressive regimen or underwent prolonged antibiotic therapy. Dual fungal and bacterial infections or superinfections have an associated mortality rate as high as 100% [41–43].

Bacterial pneumonias frequently cause fever, along with other expected clinical signs and symptoms making the diagnosis straightforward; however, in the early posttransplant phase it may be difficult to exclude noninfectious thoracic processes (i.e., pulmonary edema, atelectasis, infiltrates). If the CXR reveals abnormal patterns of infiltration, chest CT may be helpful in delineating the cause of the pneumonia. No consensus has been reached on the role of bronchoalveolar lavage (BAL) in the diagnostic evaluation, but it seems prudent for recipients with pneumonia who do not respond to antimicrobial therapy in 48 to 72 hours. No disagreement exists on the degree and rapidity with which to treat a presumed pneumonia; broad-spectrum antibiotics should be initiated immediately to cover the most common culprits mentioned earlier. Antifungals should be considered when appropriate: surveillance cultures should be obtained and reviewed to exclude the presence of multidrug-resistant (MDR) bacteria, for example, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase, and MDR *Pseudomonas* or *Klebsiella* [42,43].

The most common posttransplant infectious complication is a *urinary tract infection* (UTI), with an incidence of more than 30% during the initial 90 days posttransplant. UTIs lead to pyelonephritis and bacteremia in more than 10% of immunosuppressed KTx recipients. Gram-negative bacilli are the cause 70% of the time, but *Enterococcus*, *Staphylococcus*, and *Candida* should also be considered as possible etiologic agents. Risk factors for UTI include a history of graft dysfunction, prolonged bladder catheterization, neurogenic bladder, and ureteral surgical complications, including stent placement [44]. Treatment consists of prompt antibacterial therapy even in the cases of asymptomatic bacteruria; for persistent cases, removal of stents and a more thorough evaluation (e.g., voiding cystourethrogram, CT scan) are indicated.

A KTx, a clean-contaminated operation, carries with it a *wound infection* rate of 1% to 6%. This low rate is due to thorough pretransplant skin preparation with chlorhexidine, intravenous administration of a prophylactic antibiotic, irrigation of the urinary bladder with an antibiotic solution, and meticulous attention to hemostasis. If wound infections occur, they are treated according to standard surgical principles of drainage and antimicrobial therapy; exploration and debridement may be necessary for deep-space infections [45].

Most patients undergoing a KTx are HD-dependent and therefore have an indwelling catheter, arteriovenous fistula, or arteriovenous graft, all of which can lead to a *bloodstream infection*. The current national practice guidelines call for goal infection rates of less than 10% at 3 months after catheter placement; unfortunately, most centers fall short of that goal. Catheters should be removed when no longer required. Staphylococcal species and gram-negative bacilli are the most likely pathogens and should be treated aggressively with IV antibiotics and possibly catheter removal [46,47].

Infective endocarditis is rare but may occur in recipients with severe septicemia or longstanding immunosuppression [48]. Cardiac valve vegetations noted on an echocardiogram in recipients with persistent bacteremia confirms the diagnosis; prolonged antibiotic therapy is required.

Viral infections play a prominent role in the intermediate to late posttransplant period, predominantly the herpesvirus genus, for example, CMV, Epstein–Barr virus (EBV), herpes simplex virus (HSV), and varicella-zoster virus (herpes zoster virus [HZV]). Primary HSV infections are rare, but mucocutaneous reactivations of HSV in the early posttransplant period are relatively common, occurring in up to 30% of adult recipients and 8% of pediatric recipients. OKT3 use is associated with an even higher risk of reactivations. HSV is diagnosed by

direct immunofluorescent antibody staining, by Tzanck preparation, or by culture of tissue and body fluids. Serodiagnosis is possible if immunoglobin M (IgM) is detected or if a fourfold rise in IgG titers is noted. Symptomatic HSV infections are common with orofacial (virus resides latently in the sensory ganglia) or genital lesions; occasionally, conjunctivitis or corneal ulceration may develop. Topical application of 5% acyclovir ointment accelerates healing and shortens the duration of viral shedding; oral acyclovir (200 mg five times per day) is also effective. If disseminated disease occurs (e.g., hepatitis, meningoencephalitis), IV acyclovir (5.0 mg per kg every 8 hours for 7 to 14 days) is necessary.

CMV infections and disease, while rare during the first posttransplant month, deserve special mention because they affect a large proportion of KTx recipients at some point in their first posttransplant year. In just the initial 100 days posttransplant, up to 60% of recipients develop CMV infections (e.g., viremia), and 25% actually suffer from invasive CMV disease of one or more organ systems. Such infections are associated with chronic graft rejection and decreased graft and patient survival rates. The highest risk of developing CMV infections, up to 60%, is in the donor-seropositive, recipient-seronegative (D+ R−) group; the lowest risk, 20% to 40%, is in the D+ R+ and D− R+ groups. CMV infections may occur as primary infections (e.g., D+ R−) or as a reactivations (e.g., with a seropositive recipient after inception of immunosuppression). CMV superinfections (both primary infections plus reactivations, by separate strains of CMV) in the D+ R+ group are associated with the worst graft and patient survival rates among the various groups [49–52].

Success has been achieved in preventing CMV infections with prophylactic 9-[(1,3-dihydroxy-2-propoxy)methyl] guanine (DHPG) in parenteral (ganciclovir) or enteral (valganciclovir) forms. The efficacy of oral DHPG (valganciclovir) was found to be equal to that of oral ganciclovir in preventing CMV disease in high-risk recipients [50]. CMV disease, which is potentially (yet rarely) fatal, has not been eliminated. Symptoms include fever, malaise, headache, myalgia, and arthralgia; leukopenia occurs in more than 70% of infected recipients. CMV infections can present as neuritis, gastritis, or colitis; colitis often causes gastrointestinal tract bleeding. CMV infections can also cause retinitis, hepatitis, pancreatitis, adenopathy, hepatosplenomegaly, and nephritis, frequently during the first 6 months posttransplant.

The gold standard for diagnosis of active CMV disease continues to be growth in tissue culture; however, identification of viremia allows for much earlier diagnosis (< 48 hours) and prompt treatment. Two techniques are currently in clinical use: (1) a quantitative polymerase chain reaction assay and (2) an antigenemia assay based on identification of the late structural protein pp65. Both techniques are felt to be equally efficacious in quantifying the viral load of CMV in the serum.

When the diagnosis of CMV disease is established, treatment is initiated with IV DHPG (5 mg per kg every 12 hours if creatinine < 1.5 mg per dL, with dose adjusted according to graft function; and 1.2 mg per kg every 48 hours if the recipient is on dialysis). Dose reduction or temporary cessation of DHPG is indicated if leukopenia (white blood cell count < 3,000 cells per mm^3) or thrombocytopenia (platelet count < 100,000 per mm^3) occurs. DHPG is administered IV for 14 days; the addition of CMV hyperimmune globulin is indicated for recalcitrant and life-threatening cases. Oral DHPG treatment is frequently continued for up to 6 months. For recipients with concurrent CMV and acute rejection, simultaneous treatment is an option: IV ganciclovir should be given at the time of rejection treatment, or if possible, 1 to 2 days before increasing immunosuppression. Since cell-mediated immunity is markedly impaired during CMV infections, superinfections by other opportunistic pathogens are a risk. Graft dysfunction (e.g., glomerulopathy) during or after active CMV infections has been described. Recipients in the D+ R− (high-risk) group should receive prophylactic oral DHPG for at least 6 months posttransplant. Currently, oral DHPG is standard for CMV prophylaxis posttransplant and continues for 3 to 6 months.

Varicella-zoster virus, also called HZV, usually presents as dermatomal skin lesions. The diagnosis is frequently made on physical examination alone. HZV can be cultured, and direct immunofluorescent antibody staining or Tzanck preparation can be used. HZV requires systemic therapy with acyclovir, usually over a 7-day period. Varicella-zoster immune globulin is used in seronegative recipients.

EBV infections have been associated with mononucleosis-like symptoms and with fulminant, widespread posttransplant lymphoproliferative disease (PTLD), a form of B-cell lymphoma. Recipients of a kidney from a seropositive donor can seroconvert. Symptoms include EBV-related malaise, fever, headaches, and sore throats. PTLD usually occurs months to years posttransplant in heavily immunosuppressed recipients. Immunosuppression impairs the ability of virus-specific cytotoxic T lymphocytes to control the expression of EBV-infected transformed B cells, leading to polyclonal and monoclonal proliferation of lymphocytes (which constitutes PTLD). Treatment entails cessation of immunosuppression accompanied by anti-CD-20 antibodies (rituximab), and antiviral therapy (e.g., ganciclovir, acyclovir, or anti-CMV immune globulin). Suboptimal responses necessitate conventional lymphoma treatment.

Other viruses causing morbidity after a successful KTx are adenoviruses and influenza viruses (involving the respiratory tract), papovaviruses (progressive multifocal leukoencephalopathy), and hepatitis viruses (in particular hepatitis C). Recipients are also at high risk for developing human papillomavirus infections, which can lead to cancer of the cervix (e.g., invasive squamous cell cancer).

Fungal infections, both local and systemic, are frequent (in up to 14% of KTx recipients), and can occur early posttransplant. Most fungal infections are secondary to *Candida* and *Aspergillus* species. The most common source of *Candida* infections is translocation of organisms from the gastrointestinal tract, followed by infected intravascular catheters. Early posttransplant, *oropharyngeal candidiasis* is the most common fungal infection; it can be prevented and treated with oral nystatin or clotrimazole solutions.

Systemic fungal infections are particularly noted in recipients who are on significant immunosuppression or broad-spectrum antibacterials or who have had multiple rejection episodes and poor graft function; if such infections occur as superinfections, they are associated with a high mortality rate. Patients with cerebral, pulmonary, or visceral involvement, such as meningitis, pneumonia, or endocarditis (most frequently caused by *Candida* or *Aspergillus* species), require reduction or even temporary cessation of immunosuppression [53].

Given their favorable safety profile, the azole antifungals (e.g., fluconazole) are the preferred empiric therapy for fungal infections; however, for life-threatening fungemia, some clinicians favor the echinocandins caspofungin, the newer azole agents or amphotericin B, especially when a *Candida* species other than *Candida albicans* is suspected [54]. Liposomal amphotericin B preparations are now a more palatable option because of their improved safety profile in regards to nephrotoxicity. *Candida* can also cause an uncommon but life-threatening complication: a mycotic pseudoaneurysm. This complication is typically treated with graft nephrectomy, with or without ligation of the external iliac artery, followed by IV amphotericin B. *Cryptococcus* and *Aspergillus* can cause severe pulmonary and cerebral infections requiring systemic amphotericin B. *Pneumocystis jiroveci*, which manifests as interstitial pneumonia, usually late posttransplant [55]. Since the practice of

TMP–SMX prophylaxis was initiated, the incidence of pneumocystic pneumonia (PCP) has decreased significantly. PCP is still seen in heavily immunosuppressed recipients and should be considered in anyone with fever, dyspnea, and nonproductive cough. The CXR will reveal interstitial infiltrate; BAL or lung tissue biopsy (using staining techniques or monoclonal antibodies conjugated with fluorescein) is needed for diagnosis. Therapy consists of IV TMP–SMX (with the dose adjusted according to kidney function) and, in case of sulfa hypersensitivity, pentamidine or dapsone. PCP, like most other severe infections, requires reduction or temporary cessation of immunosuppression.

Mycobacterium tuberculosis infects about 1% of KTx recipients because of prior infections, reactivations, or disseminated disease. Fever, malaise, night sweats, and weight loss usually occur. The diagnosis should be made clinically, because only one-fourth of recipients have a positive tuberculin skin test. Sputum and blood samples should be used to identify acid-fast bacilli and a BAL may be necessary to obtain an appropriate sample. Treatment includes a 2- to 3-drug regimen lasting at least 6 months. Potential agents include isoniazid, rifampin, pyrazinamide, ethambutol, and ciprofloxacin. Despite aggressive treatment, the mortality rate can be high.

Gastrointestinal and Pancreaticobiliary Complications

The incidence of posttransplant gastrointestinal tract complications is 5% to 25%. They are a major cause of morbidity and mortality in the KTx population.

In the *upper gastrointestinal* tract, the most common problem is peptic ulcer disease and its associated complications (bleeding, perforation); evidence suggests a higher prevalence of *Helicobacter* infection in the uremic population. However, the overall incidence of upper gastrointestinal tract complications in KTx recipients has declined considerably over the last two decades, mainly because of the development and ubiquitous use of H_2 blockers and proton-pump inhibitors. Historically, severe upper gastrointestinal tract bleeding episodes occurred in more than 10% of KTx recipients, with a mortality rate of up to 65%; most of these bleeding episodes developed in the early postoperative period, half in the first 3 months [56–58].

Prophylactic gastric operations (various forms of vagotomy) became very popular in the 1970s for patients with chronic kidney failure listed for KTx, in an attempt to decrease the morbidity and mortality rates of peptic ulcer disease posttransplant. With the advent of H_2 blockers (e.g., cimetidine, ranitidine) and inhibitors of the H+–K+ adenosinetriphosphatase (ATPase) enzyme system (e.g., omeprazole, pantoprazole), prophylactic gastric operations are no longer performed [59–62].

If severe upper gastrointestinal tract bleeding occurs despite prophylactic treatment and cannot be controlled by conservative means (including gastroscopy with submucosal injection of epinephrine), the same surgical options (resection, vagotomy) apply as for nontransplant patients. Angiographic embolization for acute hemorrhage has been advocated, and, for anatomic reasons, usually requires embolization of two arteries. The risk of embolization is development of (gastric) necrosis and infection. Patients with severe upper gastrointestinal tract bleeding require ICU monitoring; it is important to stabilize them before they undergo emergency gastric procedures, which have a high mortality rate posttransplant. If extensive gastroduodenal surgery is performed, reduction of immunosuppression is mandatory and postoperative ICU monitoring recommended. An unexpectedly high incidence of CMV infections has been observed in apparent peptic ulcers in KTx recipients. Diagnostic and immunohistochemical improvements have made it easier to detect tissue-invasive CMV infections; for such recipients, DHPG and possibly anti-CMV immune globulin are initiated [63].

The impact of hypercalcemia on the pathogenesis of peptic ulcer disease and on its therapeutic consequences is controversial. Hypercalcemia due to hyperparathyroidism may aggravate peptic ulcer disease. Immediate and permanent cessation of gastric bleeding has been noted after subtotal parathyroidectomy in KTx recipients.

The most common *small bowel* complication is intestinal obstruction. Most kidney grafts are placed retroperitoneally (except in children and in recipients of a simultaneous pancreas-KTx), so obstruction is often related to previous intra-abdominal procedures (e.g., native nephrectomy, splenectomy), infections, or PTLD in the small bowel and mesentery. Obstruction in the early postoperative period may be due to incarceration of small bowel through a peritoneal tear made during retroperitoneal dissection. The same therapeutic principles apply as for nontransplant patients.

The incidence of complications of the *lower gastrointestinal tract* in KTx recipients is 1% to 10%. Colonic perforation and lower gastrointestinal tract hemorrhage are the two most common complications in the immediate posttransplant period and carry considerable morbidity and mortality if not recognized and treated expeditiously.

Colonic perforation, occurring in 1% to 2% of all KTx recipients, is due to (in descending order) diverticulitis, ischemic colitis, and CMV colitis; rarely, stercoral ulceration, fecal impaction, or an undetermined forms of colitis can result in perforation as well. The use of sodium polystyrene sulfonate, given orally or as an enema, has been implicated as a cause of perforation, but only in sporadic case reports, so the practice continues at most centers. About 50% of all colon perforations occur within the first month posttransplant, with a 20% to 38% mortality rate; risk factors for death include age older than 40 years, long-term HD, and exploration more than 24 hours from the time of initial symptoms. Peritoneal signs, the hallmark of hollow organ perforation, are frequently absent in immunosuppressed KTx recipients, mandating a high index of suspicion, liberal use of imaging studies, and a low threshold for exploration; in general, a diverting colostomy has been associated with better outcomes [64–73].

KTx recipients are more susceptible to *colonic diverticulitis* and tend to more readily perforate, as compared with nontransplant patients; KTx recipients with polycystic kidney disease are at even higher risk [74–76]. Steroids are thought to be responsible for the difference in the incidence of diverticulitis between transplant recipients and nontransplant patients; steroids not only mask symptoms but also impair the host's ability to localize and contain the perforation. Furthermore, steroids adversely affect colon wall microcirculation and weaken peritoneal defense mechanisms. Historically, diverticular perforations have been associated with prohibitive (50% to 100%) mortality rates, but a series showed a marked decrease in mortality (12.5%), thanks to increased awareness of the problem and prompt surgical intervention. Recipients with sigmoid diverticulitis require resection of the sigmoid colon, with creation of a colostomy and Hartmann pouch; at least one group of investigators advocates a primary anastomosis and a loop colostomy in appropriate cases. Some transplant surgeons advise a pretransplant partial colectomy for KTx candidates who experience a single episode of documented diverticulitis; however, no consensus has been reached.

Ischemic colitis has been associated with impaired blood flow to the colonic wall, stenosis or occlusion of the inferior mesenteric artery, insufficient vascular collateralization, previous retroperitoneal surgery, immunosuppressive and antibiotic therapy, and diseases such as vasculitis and

thrombophilia. Other causative factors are (intermittent or temporary) hypotension and irregular blood volume distribution. Often, however, no explanation is apparent, especially in young KTx recipients with normal mesenteric vessels. Ischemic colitis may be segmental or pancolic; at laparotomy, features suggestive of inflammatory bowel disease may be identified that microscopically lack the typical lesions of Crohn's disease [77,78].

Pseudomembranous colitis caused by the *Clostridium difficile* species is being increasingly recognized, to enhanced surveillance; it can progress to toxic megacolon and perforation. The diagnosis is confirmed via stool toxin assay and culture, or with visualization of the classic pseudomembranes on endoscopy. Such recipients are usually treated conservatively, with metronidazole (250 mg four times daily for 10 days) or oral vancomycin (125 mg every 6 hours for 10 days).

Neutropenic enterocolitis causes mucosal ulceration of the bowel wall. It is associated with profound neutropenia and invasion by clostridial organisms (e.g., *Clostridium septicum*). The course of neutropenic enterocolitis is often progressive, requiring treatment with metronidazole and possibly surgical intervention [79]. *Infectious colitis* is frequently due to CMV infections, which may cause lower gastrointestinal tract hemorrhage; at stated before, CMV rarely is clinically active within the first posttransplant month. Infectious colitis can also be bacterial (e.g., mycobacteria), viral (e.g., herpes), and fungal (e.g., *Candida*) infections. The diagnosis is obtained via endoscopic biopsy and stool cultures, with treatment starting with appropriate and early empiric antimicrobial agents. Surgical intervention is not desirable, given the increased morbidity and mortality rates.

Cecal volvulus is a rare complication but requires prompt surgical intervention [80]. If gangrene is not evident, a cecopexy can be performed; if a perforation has occurred, resection and creation of a colostomy are imperative.

The incidence of posttransplant *acute colonic pseudo-obstruction (Ogilvie's syndrome)* is 1.5% [81]; it causes paralytic colonic ileus resulting in cecal dilation. Usually, it responds to nonoperative therapy consisting of bowel rest and nasogastric decompression, neostigmine, and possibly endoscopic colonic decompression. Like fecal impaction and stercoral ulceration, Ogilvie syndrome can cause colonic perforation, thus necessitating surgical resection. In general, survival rates in recipients with colonic perforation can be improved with early diagnosis and prompt treatment. As with treatment for septicemia, immunosuppression should be markedly reduced. Of interest, rejection in recipients with severe infection is not common. Once the recipient's condition improves, immunosuppression should cautiously be restarted.

Lower gastrointestinal tract *hemorrhage* is most commonly due to opportunistic colitis. Gastrointestinal tract lesions thought to be peptic, particularly when associated with upper gastrointestinal tract bleeding, are frequently the result of CMV infections [82]. Fungal ulceration has also been described as a source of lower gastrointestinal tract hemorrhage, because proton-pump inhibitors, H_2 blockers, and antacids promote fungal overgrowth due to achlorhydria. Another cause of lower gastrointestinal tract bleeding is the ulcerogenic effect of steroids and their tendency to impair the reparative mechanisms of the bowel wall. In addition, conditions such as uremia and diabetes result in colonic distention and impaction, because of autonomic neuropathy; both contribute to the pathogenesis of colonic ulcers. In recipients with lower gastrointestinal tract bleeding, colonoscopy must be undertaken urgently, so that treatment is not delayed. To prevent fungal superinfection dissemination, empiric fluconazole is initiated.

KTx recipients are exposed to numerous risk factors for pancreatitis: (1) immunosuppressants (e.g., corticosteroids, azathioprine, cyclosporine) and diuretics (e.g., furosemide, thiazide diuretics); (2) hypercalcemia with or without hyperparathyroidism [83]; (3) infections (e.g., CMV, HSV) [84]; (4) previous episodes of pancreatitis (uremia); and (5) cholelithiasis (i.e., related to cyclosporine). Therefore, it is hardly surprising that 1% to 6% of recipients suffer a posttransplant episode of pancreatitis. The mortality rate appears to be highest if pancreatitis develops after the first three posttransplant months [85]. Steroids increase the viscosity of pancreatic secretions (theoretically leading to obstruction and dilation of the pancreatic duct) and speed epithelial duct proliferation and peripancreatic fat necrosis. An equally serious side effect of steroids is that they mask abdominal pain during episodes of pancreatitis, thus delaying the diagnosis. Hypercalcemia secondary to tertiary hyperparathyroidism is also considered a major causative factor; excessive serum calcium concentration accelerates the conversion of trypsinogen, promoting pancreatic autodigestion. Infections, especially CMV, are a well-documented cause of posttransplant pancreatitis, but bacterial infections causing pancreatitis have also been reported. The term *rejection pancreatitis* arose from speculation that the host forms antibodies that are reactive not only with the graft (vascular rejection), but also with antigens on the surface of pancreas cells (vascular pancreatitis). Biliary tract disease and alcoholism, the most frequent causes of pancreatitis in nontransplant patients, are of minor importance in KTx recipients [86–89].

The diagnosis of pancreatitis depends mainly on an observed increase in the serum amylase or lipase level. However, hyperamylasemia in uremic recipients is not uncommon (30%), because of reduced amylase clearance in light of insufficient kidney function. The amylase/creatinine clearance ratio appears to be a more sensitive index of pancreatitis in KTx candidates with kidney dysfunction. The degree of hyperamylasemia is not a prognostic factor. A contrast-enhanced CT scan may be helpful in both staging pancreatitis and excluding necrotizing pancreatitis. For the edematous form of pancreatitis, conservative treatment is usually successful. Recipients with hemorrhagic or necrotizing pancreatitis require ICU monitoring, with specific attention to volume replacement and cardiovascular status. In such recipients, reduction of immunosuppression, use of broad-spectrum antibiotics, and ICU monitoring are imperative.

The role of early surgical intervention is still controversial. Recipients with infected pancreatic necrosis are best served with aggressive surgical therapy, including removal of all infected necrotic material, drainage and irrigation of the abdominal cavity, and a low threshold for relaparotomy. Overwhelming sepsis is the most common cause of death, so intensive management of infections is essential. Surgical intervention is also required if pseudocysts develop and do not resolve, although maturation of pseudocysts may take longer in KTx recipients. Pseudocyst complications, such as erosion or obstruction of adjacent vascular and hollow viscus structures, mandate early intervention. The mortality rate from complications of posttransplant pancreatitis appears to be higher than from other forms of pancreatitis. A rapid reduction of immunosuppression is necessary to minimize septic complications.

Pretransplant screening for *cholelithiasis* is variably performed at centers in the United States: the role of prophylactic cholecystectomy for asymptomatic cholelithiasis is controversial. Data generated over the past 15 years failed to strengthen a policy of mandatory pretransplant cholecystectomy for asymptomatic cholelithiasis. *Acute cholecystitis*, especially in uremic diabetic KTx recipients, should be considered if they have sepsis or abdominal pain without a source. *Acalculous cholecystitis* has become more common in recipients with a complicated posttransplant course (e.g., septicemia, multiorgan failure). This diagnosis is established clinically and, especially if recipients are intubated and on the ventilator, by serial ultrasounds and possibly biliary scintigraphy. A cholecystectomy is

desirable, but image-guided (ultrasound or CT) cholecystostomy may also be helpful if recipients are too ill to undergo a formal operation [90,91].

Neurologic Complications

Up to 30% of KTx recipients develop neurologic problems posttransplant. The incidence of life-threatening central nervous system (CNS)-related complications in the immediate posttransplant period is 1% to 5% [92–94]. Causative factors are the sequelae not only of the KTx itself, but also of the underlying kidney disease (more common in recipients with diabetes and hypertension) and of pretransplant conditions (e.g., uremia). *Cerebrovascular events* (e.g., infarct, TIA, hemorrhage) are the most frequent complications, usually peaking during the first few months posttransplant. Hypertension, atherosclerosis, diabetes, hyperlipidemia, hypercoagulability, and advanced age—all of which play a major role in the pathogenesis of these complications—are ubiquitous in KTx recipients. For those with strokes or TIAs, conservative treatment (heparinization, aspirin) is best, although carotid endarterectomy can benefit those with ulcerated carotid lesions or with severe but accessible stenoses. The prognosis of intracerebral hemorrhage is poor; posttransplant hypertension is one of the major causative factors and therefore should be aggressively monitored and treated.

All CNS *infections* are considered life threatening, and often result in various degrees of disability. Infections are caused by bacteria (e.g., *Listeria monocytogenes*, *Pseudomonas* species), viruses (e.g., CMV, HSV), fungi (e.g., *Cryptococcus, Aspergillus, Mucor*), and parasites (*Toxoplasma*). *L. monocytogenes* is the most common infectious organism and usually causes meningitis. *Aspergillus* frequently manifests as brain abscesses. Rhinocerebral mucormycosis infection can cause cavernous sinus thrombosis and rapid death. Dissemination of CMV may include the CNS, although the overall incidence is low [95]. Acute polyradiculoneuritis has also been associated with CMV infections [96]. Similarly, dissemination of the VZV can involve the CNS [97] or facial nerve (Ramsay Hunt syndrome). It is crucial to diagnose and treat these infections early and aggressively. Intrathecal administration of antimicrobial drugs or drainage in recipients with brain abscesses may be necessary.

Seizures are associated with excessively high CNI serum levels and affect children at a higher frequency than adults; hypertension and hypomagnesemia may predispose recipients to seizure activity [97–101]. Treatment consists of CNI dose reduction and anticonvulsants; ICU monitoring is mandatory after such events. Other CNI-related complications, such as tremor, dysesthesia, ataxia, and psychologic disorders, usually do not require ICU monitoring. Tacrolimus, more frequently than cyclosporine, causes neurotoxicity in the form of tremor and headaches, both of which can be debilitating; it also can cause paralysis, quadriplegia, coma, and leukoencephalopathy (*posterior reversible encephalopathy syndrome* [PRES]). PRES, occurring in about 0.35% of KTx recipients, is diagnosed by brain magnetic resonance imaging [102]. Another drug-related complication is aseptic meningitis caused by OKT3; treatment consists of discontinuing OKT3 therapy and temporarily administering anticonvulsants.

In contrast to CNS-related problems, peripheral neurologic complications do not require ICU monitoring. Compressive *neuropathy* (involving the femoral nerve or the lateral femoral cutaneous nerve) is due to hematoma, ischemia, or retraction injury at the time of the KTx; all symptoms are confined to the ipsilateral side. This complication has a high degree of reversibility [103]. If a large hematoma is identified, reexploration and evacuation should be performed.

TABLE 182.1

CURRENT CHALLENGES IN KIDNEY TRANSPLANTATION

Clinical dilemma	Management
Higher acuity KTx waiting list Age > 50: 58% Diabetic: 28% Hypertensive: 22% Waiting list mortality Organ scarcity Sensitized recipients	Exhaustive pretransplant evaluation Intense posttransplant critical care and subspecialty consultation Innovative recipient immunomodulation Desensitization protocols Complement modulation Live donor paired kidney exchange National live donor registries

KTx, kidney transplantation.

CURRENT CHALLENGES IN KIDNEY TRANSPLANTATION

Despite the many advances in kidney transplantation, several challenges remain (Table 182.1). During the past decade the proportion of candidates on the active KTx waiting list > 50 years of age has increased from 44% to 58% and those with diabetes and hypertension have increased from 24% to 28% and 17 to 22%, respectively. To maintain excellent short-term outcomes, an exhaustive pretransplant cardiovascular evaluation followed by intense posttransplant critical care has become mandatory for this high-acuity cohort of patient [6,7].

Mortality on the waiting list continues to stimulate the adoption of innovative desensitization protocols to allow high-risk recipients an opportunity at transplant. This in turn must be met with equally innovative therapies if antibody-mediated rejection occurs in the early postoperative period. Attempts at modulating the complement system are underway to mitigate early posttransplant injury in the allograft [14].

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CHAPTER 183 ■ SPECIFIC CRITICAL CARE PROBLEMS IN HEART AND HEART–LUNG TRANSPLANT RECIPIENTS

SARA J. SHUMWAY AND EIAS E. JWEIED

The advent of thoracic organ transplantation has brought new hope to patients who were previously doomed by end-stage cardiac, pulmonary, or combined cardiopulmonary disease. The first heart transplant was performed on December 3, 1967. Fourteen years passed before the first successful heart–lung transplant was performed on March 9, 1981. Heart–lung transplantation established the potential for lung transplantation as a viable therapeutic option, and the first successful single-lung transplant was performed in 1983 [1].

HEART TRANSPLANTATION

The United Network for Organ Sharing (UNOS) is a nonprofit organization that maintains the nation's organ transplant waiting list. Patients awaiting cardiac transplants are listed according to severity of illness. Organs are then allocated to those individuals who are severely ill and have waited the longest. Just more than 2,200 heart transplants are performed annually in the United States. There has been a decrease in candidate waiting times, with the average waiting time for a status 1A heart candidate of 50 days and a status 2 candidate of 309 days [2]. A status 1 heart candidate includes those individuals with highest medical urgency. These are patients who have support either via a total artificial heart, ventricular assist device (VAD), intraaortic balloon pump, or extracorporeal membrane oxygenation. It could also be an individual who has a mechanical assist device in place, either right or left support that is beginning to malfunction. It also includes individuals who are on continuous mechanical ventilation or on high-dose inotropic support and are unable to be weaned. Status 2 candidates are individuals who need a heart transplant but have not been defined as being in the most urgent status. They may be patients who are at home and taking heart-failure medications and are still active

and awaiting transplant but are not as critically ill as those individuals in the status 1 category. At any given time, UNOS has approximately 3,000 candidates listed for heart transplant, and most have been waiting for more than a year.

The number of heart transplants performed nationally depends on donor availability. In spite of this, the annual mortality rate on the waiting list has slowly declined during the last 10 years. In the middle to late 1990s, it was not uncommon to have anywhere between 700 and 800 people die from cardiac disease while awaiting a heart transplant. That number has been slowly decreasing to less than 400 each of the last 3 years [2]. This slow decrease is related to the evolution of left ventricular assist devices and their acceptance as a bridge to transplant.

Ninety percent of adult candidates listed for heart transplant have end-stage cardiac disease with some form of cardiomyopathy. Approximately 47% have idiopathic cardiomyopathy, and 35% have ischemic cardiomyopathy. The remaining 15% of heart transplant candidates have end-stage valvular disease, cardiomyopathy associated with congenital heart disease, or graft failure requiring retransplantation. Cardiac retransplantation represents approximately 4% of the adult heart transplant population annually [2,3].

Patient Selection

Many of the specific critical care problems seen in thoracic organ recipients can be reduced by careful patient selection. In well-compensated patients, a weeklong outpatient evaluation is performed. This applies to approximately 80% to 90% of patients seen at a cardiac transplant center. The other 10% to 20% are individuals who are desperately ill and undergo an urgent transplant evaluation.

The recipient assessment consists of a general evaluation, an assessment of the functional and hemodynamic status, and a psychosocial evaluation. All parts are equally crucial. One of the first assessments is an oxygen-consumption treadmill test. For those patients who are capable of performing this test, there are excellent data that demonstrate that a peak oxygen consumption of less than 12 mL per kg per minute is associated with a very poor 1-year survival rate without transplant. Individuals with a peak oxygen consumption of less than 15 mL per kg per minute should be considered for listing [4,5]. The assessment then proceeds with a general evaluation. The patient's medical history is examined to try to determine the cause of the patient's heart disease. General laboratory tests are performed, including a creatinine clearance. Individuals who have a creatinine clearance of less than 50 mL per minute do have a significant increase in the need for postcardiac transplant dialysis and a decrease in survival rate. Individuals with severely abnormal creatinine clearance would be excluded from heart transplant or considered for heart and kidney transplantation. Individuals with diabetes need further end-organ evaluation prior to listing to understand the full scope of their risk.

Nutritional status is also crucial. Those individuals with a body mass index less than 20 kg per m^2 or greater than 35 kg per m^2 would be asked to either gain or lose weight, respectively. Again, individuals at the extremes of the body mass index have an associated increase in postoperative mortality [6,7].

The hemodynamic evaluation consists of an echocardiogram to evaluate function and anatomy, and a cardiac catheterization. The cardiac catheterization includes evaluation of heart function by a right heart catheterization as well as a coronary angiogram. In this assessment, the patient's coronary anatomy is examined for potential intervention, and any abnormalities in the filling pressures, pulmonary capillary occlusion pressure, or pulmonary vascular resistance are identified.

Patients with heart failure and secondary pulmonary hypertension are a group who are of special interest. Pulmonary arterial and capillary wedge pressures are measured to determine the degree to which a patient has secondary pulmonary hypertension and whether or not it is reversible. The patient's hemodynamics should be optimized in the catheterization laboratory in an attempt to decrease the pulmonary arterial pressures to normal levels, and 100% oxygen, nitric oxide, and other pulmonary vasodilators can be used to test for reactivity in the pulmonary bed. The absolute exclusion criteria for heart transplantation are a pulmonary vascular resistance greater than 4 Wood units (WU) and, more importantly, a transpulmonary gradient greater than 15 mm Hg. Individuals with values outside these values would then be listed for heart–lung transplant, or be given a trial of pulmonary vasodilators.

The patient's ABO blood type and panel-reactive antibody (PRA) level is determined to quantitate the patient's preexisting antibodies and sensitization to the general population. If class II (locus D) is greater than 20%, it is recommended that a preoperative cross-match be performed. The patient's HLA typing is also done at that time, and if the PRAs are significantly elevated, the laboratory should be able to identify the particular human leukocyte antigen to which the individual is reacting. Sensitization can occur in many situations. It may occur because of pregnancy, between sexual partners, from prior transplantation, or with transfusions often associated with the placement of a ventricular assist device. Individuals who carry a high PRA level have been treated in the past with plasmapheresis, intravenous immunoglobulin, cyclophosphamide, and mycophenolate mofetil (MMF). There have been inconclusive results with each of these.

The psychosocial evaluation should be centered on evaluating not only the transplant recipient but also the family support for the patient. This needs to be performed by a social worker and, when indicated, other mental health professionals who have a keen understanding of the demands made on a postoperative cardiac transplant patient. Patients need to be medically compliant, have adequate neurocognitive function for the postoperative regimen, and adequate social support.

Once the evaluation has been completed, the patient is evaluated for any relative or absolute contraindication for heart transplant. Those relative contraindications include age greater than 70 years, previous chronic substance abuse, limited social support, limited adaptive ability, mild renal dysfunction, active peptic ulcer disease, cachexia, obesity, and cigarette smoking. It should be noted that to receive a heart transplant, individuals who smoke are required to go through a smoking-cessation program, and many transplant programs require them to sign a contract stating that they will not resume smoking prior to or after the transplant. They also are evaluated for chemical evidence of smoking during their waiting time [8].

Absolute contraindications to cardiac transplantation include ongoing substance abuse, refractory psychiatric conditions, suicidal behavior, severe personality disorder, issues with ongoing medical noncompliance, inadequate neurocognitive ability, irreversible hepatic or renal dysfunction, severe peripheral or cerebral vascular disease, systemic disease that limits rehabilitation, insulin-dependent diabetes with severe end-organ damage, and evidence of severe, fixed, secondary pulmonary hypertension [8–10].

Implantable Cardiac Assist Devices

The proliferation and success of ventricular assist devices probably represent the greatest advance in the treatment of end-stage heart failure and the field of heart transplantation of the past 10 years (Table 183.1). With an assist device implanted, patients who would otherwise not survive long enough to

TABLE 183.1

ADVANCES OF VENTRICULAR ASSIST DEVICES IN HEART FAILURE TREATMENT

Topic	Finding	Reference
Destination therapy trial with pulsatile pumps	Improved survival at one year with mechanical assist device vs. medical management for Class III and IV heart failure	[11]
Bridge to transplant trial with continuous flow pumps	HeartMate II provides effective support to transplant for at least 6 months with 75% survival	[12]
Improved survival with continuous flow pumps	Effective support, improved functional status and quality of life with 72% survival at 18 mo	[48–50]

receive a heart transplant are now living independently at home with reasonably good quality of life until a suitable organ becomes available. Today, at high-volume heart transplant centers, many if not most patients arriving for heart transplantation have an assist device already in place and it can be expected that in the coming years most if not all heart transplant recipients will have had one of these devices implanted by the time they receive an organ.

From their increased use, a corpus of terminology has evolved to categorize and describe the devices themselves, their use, and technical aspects of their function and performance. Most devices are designed to assist the left ventricle and hence are called left ventricular assist devices (LVADs). However, some models are made to be implanted in either ventricle and when implanted on the right side are referred to as a right ventricular assist devices (RVAD). When both ventricles are mechanically assisted, each with its own pump, the whole system together is referred to as a biventricular assist device, or BIVAD.

There are two broad categories of devices in use based on pump mechanism: pulsatile devices that employ some type of pneumatic pump, and continuous, or axial, flow devices that involve a spinning propeller. The cycles of the pulsatile device are measured in beats per minute (bpm) and that of the continuous flow pumps in revolutions per minute (rpm). Each device has an inflow cannula through which the patient's blood is drawn from the heart and into the pump and an outflow cannula that directs the blood back into the patients' circulation.

Further, for both pulsatile pumps and continuous flow pumps, there are two more classifications that can be described on the basis of the location of the pump when implanted: intracorporeal wherein the entire pump is implanted inside the body with the exception of the drive-line that powers the device and passes through an exit site on the abdomen; the other is paracorporeal, or extracorporeal, wherein the pump sits outside the body and the inflow and outflow cannulae enter and exit the skin on the upper abdomen just below the costal margin.

Most LVADs usually involve an inflow cannula placed in the apex of left ventricle and the outflow cannula in the ascending aorta. The only permanent RVAD approved for use in the United States is the Thoratec® Paracorporeal Ventricular Assist Device and its inflow cannula is placed in the right ventricular free wall and the outflow cannula is anastomosed to the pulmonary artery. The Levitronix® CentriMag (now owned by Thoratec®) is approved for temporary right ventricular assistance up to 30 days and its inflow cannula may be placed in either the right atrium or the right ventricle.

Lastly, there is a categorization of devices based upon the intended therapeutic goal for each particular patient. Bridge to transplant (BTT) indicates that the patient is or will become a heart transplant candidate and the device is intended to improve survival and other physiologic parameters until an organ is available. Destination therapy (DT) indicates that the patient is not a transplant candidate but the device is implanted to improve survival and quality of life for the remainder of the patient's life. Bridge to recovery refers to the patient who is expected to recover from heart failure and the device is used to sustain life until the time when it can be weaned off and explanted. Bridge to decision (BTD) refers to those patients for whom survival is not certain and a temporary assist device, such as the AbioMed BVS5000™ or the Levitronix® CentriMag, is used in the critical care setting to prolong life until it can be determined whether the patient ought to be implanted with a long-term device as those used in BTT or DT patients or be disconnected from the BTD device and allowed to expire.

The superior efficacy of VADs over optimal medical management in improving survival in end-stage, New York Heart Association Class 3 or 4 heart failure patients was proven in the REMATCH trial: patients implanted with the Thoratec® HeartMate VE had a 52% survival at one year compared to 25% in the medically managed group [11]. Subsequently the Food and Drug Administration (FDA) approved the HeartMate XVE for destination therapy. The Thoratec® HeartMate II continuous flow pump demonstrated efficacy in bridge to transplantation with 75% survival at 6 months postimplantation and 68% survival at 1 year [12]. It received approval by the FDA in April 2008 for bridge to transplantation and was subsequently approved for destination therapy in January 2010. Smaller devices such as the Jarvik 2000 Flowmaker™ and the HeartWare™ VAD are currently under investigation in the United States with more than two dozens other devices presently in development (Fig. 183.1).

Knowing how these devices work and how these patients are managed will be an important part of the pretransplantation care of the recipient, and indeed any critically ill patient who is admitted with one of these devices. Almost all of these patients will arrive anticoagulated on warfarin. It will be important not to begin administration of plasma and cryoprecipitate until the plan to proceed with the transplant is certain. Administration of blood products without completing the transplant will only sensitize the recipient and increase the PRAs for any subsequent transplant offers [13]. The postoperative course is often complicated by bleeding. Drains for the VAD pocket are necessary and pericardial effusions are more common.

Several studies have examined posttransplant survival and recent studies have shown that recipients of ventricular assist devices have had equal or better posttransplant outcomes [14,15]. One exception is the patient who had VAD-related sepsis prior to transplantation as these patients had a trend to slightly poorer posttransplant survival than those patients who did not have an infection [16].

Donor Criteria

The donor evaluation begins with the pronouncement of brain death. The local organ procurement agency will obtain consent

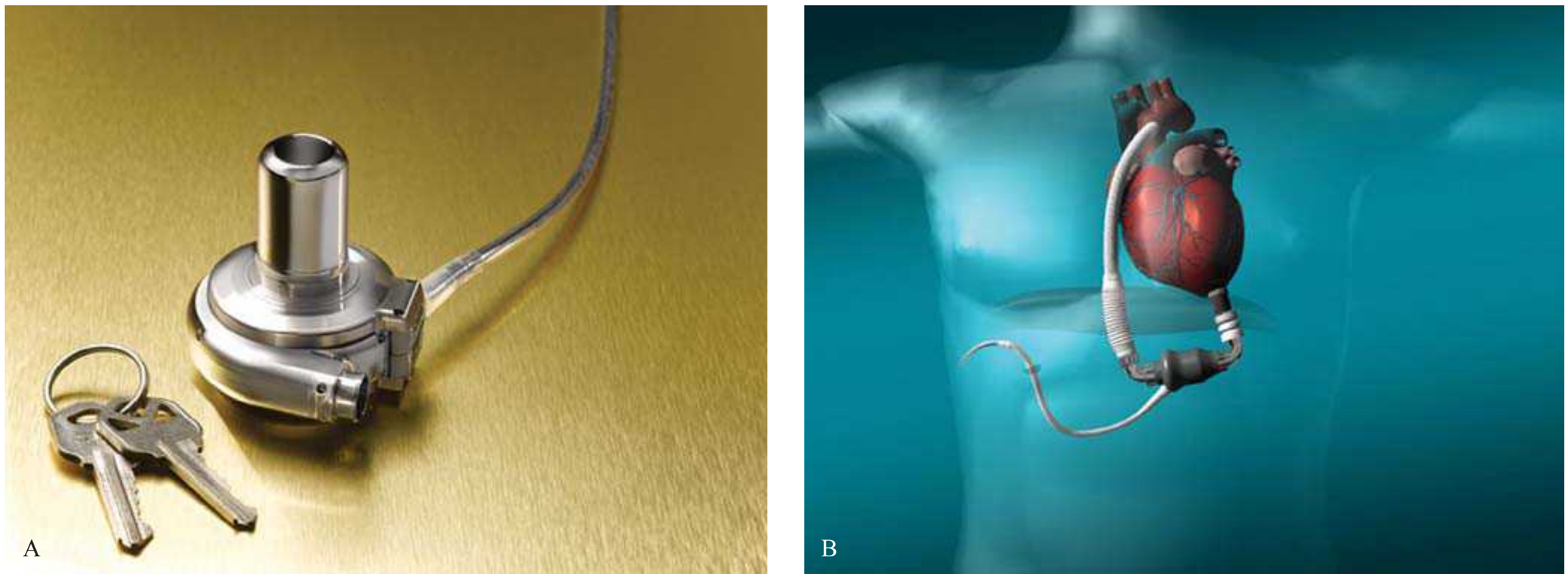

FIGURE 183.1. Continuous flow ventricular assist devices. **A:** HeartWare ventricular assist device. [Reprinted with permission from HeartWare™.] **B:** HeartMate II ventricular assist device. [Reprinted with permission from Thoratec®.]

for donation from the family and proceed with the donor evaluation and support. The donor evaluation consists of taking a general history of any illnesses or risk factors such as heart disease, hypertension, diabetes, or cigarette smoking. Specifics are gathered surrounding the time and mode of death to determine whether there is any potential cardiac injury, down time, cardiopulmonary resuscitation, or cardioversion. The organ-procurement professionals will proceed with a hemodynamic evaluation of the patient. This consists of at least measuring central venous pressures and, potentially, full hemodynamic profiles if pulmonary artery catheter measurement capability exists at the donor hospital. Once the donor is stabilized hemodynamically, further studies are performed. The initial stabilization phase should include endocrine support with the administration of levothyroxine and corticosteroids, reduction of inotropic support if it is appropriate, and, potentially, diuresis or transfusion if needed. A surface echocardiogram is then performed to make sure the heart is structurally normal and that function is normal. A 12-lead electrocardiogram is also obtained. It is not uncommon to find subtle ST changes in individuals who are brain-dead. It is generally accepted that a cardiac catheterization will be necessary in male donors more than 40 years old and female donors more than 45 years old, but catheterization should also be performed in younger donors if the donor has a significant history of hypertension, cigarette smoking, diabetes, or alcohol abuse. Cardiac enzymes need to be carefully evaluated and correlated to any severe hemodynamic instability, the use of cardiopulmonary resuscitation, as well as the time of herniation [17].

A number of studies have demonstrated correlations between elevations of troponin and early graft failure [18,19]. In one study, a cardiac troponin I value greater than 1.6 μg per L was a predictor of early graft failure, with a sensitivity of 73% and a specificity of 94% [18]. These data should be analyzed closely with the patient's hemodynamic function and echocardiographic findings.

A transplant center may request that a second echocardiogram be performed if the first echocardiogram was performed shortly after herniation. Catecholamine-induced left ventricular dysfunction can improve significantly in a short period of time and not preclude excellent short- and long-term outcomes. One must also take into consideration the ischemic time that will be incurred with procurement and travel time. The majority of transplant centers are willing to accept an ischemic time up to 4 hours for adult donors but no more than 6.

Operative Techniques

Donor Operation

Once the donor has been prepared and the abdominal team has started their procedure, the median sternotomy incision is performed. If lungs are being harvested, both pleural spaces are also opened for inspection of both lungs. During this inspection, one should palpate the coronaries to discern any calcifications and also palpate the aortic root for calcifications. External evaluation of the heart is not a reliable evaluation of function unless there is something grossly abnormal, such as severe bruising from a myocardial contusion or a dilated right ventricle. Once it is determined that the heart is appropriate for transplantation and all of the other organ teams are ready, the donor is heparinized and cannulated. The heart is cannulated with a cardioplegia cannula in the ascending aorta. If the lungs are being harvested, a pulmonary artery cannula will be placed in the main pulmonary artery. Once all teams are ready, the aorta is cross-clamped and the flush solution is given. Between 1 and 2 L of cold cardioplegic solution are administered. The heart is vented via the left atrial appendage, excised, and is then submerged in ice slush saline, packaged sterilely, and placed in a cooler for rapid transport to the recipient center.

Recipient Operation

Once the recipient is prepared and draped, the median sternotomy incision is made and the heart is dissected free of any adhesions, and then cardiopulmonary bypass is established.

The recipient is placed on total cardiopulmonary bypass, before the cross-clamp is applied the aorta, and the heart is excised along the atrioventricular groove. The great vessels are divided just above their respective semilunar valves. The anastomoses are performed in the following order: left atrial, right atrial or inferior vena caval, pulmonary arterial, aortic, and, if bicaval anastomoses are being performed, superior vena caval

[20]. Temporary pacing wires are left on the donor right atrium and right ventricle. The organ is reperfused and, once it has recovered, separated from bypass. On separation from bypass, the appropriate inotropic support is administered. Typically, the patient may require dopamine or epinephrine and milrinone for postoperative support. Isoproterenol is used to maintain an appropriate heart rate if bradycardia is a problem or the heart is paced. The pulmonary artery catheter should be floated through the new heart so that pulmonary artery pressures can be monitored closely and any signs of right heart failure can be detected early.

Postoperative Care

The immediate postoperative management of a heart transplant recipient is by and large not unlike that of other cardiac surgery patients. Drips and temporary pacing leads are modified to optimize cardiac index and end-organ perfusion. Typical inotropes used are epinephrine, dopamine, dobutamine, and milrinone. A pulmonary artery catheter is used with continuous mixed venous oximetry and preload is optimized with either volume or diuretic. Usually patients come out of the operating room on Isuprel (isoproterenol) to stimulate the heart rate and/or the temporary pacemaker set to a back-up rate of 90 to 100 bpm or higher. The ideal heart rate for these patients in the first few days postoperatively is 100 to 120 bpm. After the first several days, the heart rate is allowed to drift to its baseline as the cardiac index allows. Occasionally, patients exhibit a distributive shock immediately postoperatively characterized by low systemic vascular resistence and vasopression or neosynephrine are used to treat it.

Ventilatory management varies from patient to patient. The ideal patient who is hemodynamically stable and has no signs of surgical bleeding can be extubated within a few hours. Sometimes patients with right ventricular failure due to pulmonary hypertension need to be treated with inhaled nitric oxide or epoprostenol (Flolan®) and thus mechanical ventilation is continued.

Patients who have had a ventricular assist device placed as a bridge to transplant frequently have had two or more prior sternotomies and arrive to the hospital on Coumadin. These patients have a tendency to bleed more postoperatively and one should keep a low threshold to return to the operating room for exploration if bleeding persists.

Serious ventricular failure after cardiac transplantation is unusual and can be related to poor donor-organ selection, poor graft preservation, a long ischemia time, or rejection due to the presence of preformed antibodies. Early rejection is often heralded by atrial fibrillation and the manifestation of arrhythmias should prompt an immediate work-up and treatment. Plasmapheresis can be very effective in removing preformed antibodies responsible for humoral rejection. Inotropes and pulmonary vasodilators are also often used to manage the right heart failure that frequently accompanies rejection, with the addition of an intra-aortic balloon pump if necessary. In cases of severe graft dysfunction, ventricular assist devices can support the patient until either the donor heart recovers or retransplantation takes place.

Immunosuppression

Balanced triple-drug immunosuppression is still the most commonly used protocol, consisting of calcineurin inhibitors, an antimetabolite, and corticosteroids (Table 183.2). The calcineurin inhibitors include cyclosporine and tacrolimus. Cyclosporine is largely recognized as the agent that moved cardiac transplant from a feasible medical option to an acceptable medical treatment. The physicians at Stanford University performed a randomized control trial in cardiac transplant patients that demonstrated that cyclosporine immunosuppression improved 1-year survival to 80% from the mid-50% range [21]. Patients receiving either cyclosporine or tacrolimus have similar survival rates in heart transplantation, both long and short term [22–24]. However in a controlled clinical trial by Kobashigawa et al. in 2006 studying 343 de novo cardiac transplant patients, tacrolimus in combination with either mycophenolate or sirolimus had fewer occurrences of grade 3 A or greater rejection or hemodynamic compromise rejection at 1 year when compared to cyclosporine and mycophenolate [25]. In addition, median serum creatinine and triglyceride levels were lowest in the tacrolimus and mycophenolate group. Cyclosporine is well known to also cause postoperative hypertension, nephrotoxicity, hepatotoxicity, gingival hyperplasia, hypertrichosis, and tremor. Tacrolimus also causes nephrotoxicity and many of the other side effects of cyclosporine but to a lesser extent, in particular, posttransplant hypertension and gingival hyperplasia.

The antimetabolites include MMF and azathioprine. These inhibit purine synthesis and thus block proliferation of both T and B cells. They are complimentary to the calcineurin inhibitors. Kobashigawa et al. [26] demonstrated considerable benefits to MMF over azathioprine when coupled with cyclosporine in transplants performed in 1998. MMF is current the most widely used antimetabolite in heart transplantation [24].

Corticosteroids remain a cornerstone of therapy. There are multiple regimens for early corticosteroid reduction to avoid the serious side effects of corticosteroids. These include systemic hypertension, obesity, osteoporosis, and glucose intolerance. In spite of the negative side effects, in 2004 approximately 75% of patients were still taking corticosteroids 1 year following their transplants [27]. Monotherapy consisting of tacrolimus is currently being studied in heart transplant recipients. In one study, 75% of recipients were successfully converted to monotherapy [28] and other prospective randomized clinical trials are currently underway to evaluate these findings.

The use of IL-2 receptor blockade has become more prevalent during the last 4 to 5 years. These proliferation signal inhibitors, sirolimus and everolimus, block the activation of the T cell via the engagement of the IL-2 receptor. They have shown promise in significantly reducing the severity of cardiac allograft vasculopathy, the main threat of long-term graft survival. But they remain only a compliment to the calcineurin inhibitors that are still more effective in preventing acute rejection.

Outcomes

The registry of the International Society for Heart and Lung Transplantation (ISHLT) has reported on survival after cardiac transplantation in adult patients transplanted from 2004 to 2008, with survival rates of 85% to 89% at 1 year [29]. The UNOS/OPTN (Organ Procurement and Transplantation Network) database also report survival rates at 1 year of 87.7%. These data were from patients transplanted from 1997 to 2004 [2].

Over the years, the average survival rate for cardiac transplant patients improves. The median survival in patients who were transplanted between 1982 and 1988 was 8.1 years, and that has increased to 9.8 years for individuals transplanted between 1994 and 1998. A significant improvement that has occurred during the current era is the 1-year survival for cardiac retransplantation, which is markedly better than that reported in past eras. The 1-year survival for these patients is 82.4% [2].

TABLE 183.2

BALANCED TRIPLE-DRUG IMMUNOSUPPRESSION PROTOCOL[a]

Drug	Perioperative	Maintenance	Taper	Maintenance	Withdrawal
Corticosteroids					
Methylprednisolone	10 mg/kg intraoperatively or perioperatively; 125 mg IV q8 h three doses postoperatively				
Prednisone	0.5 mg/kg IV/PO qd in two divided doses	0.5 mg/kg IV/PO qd in two divided doses	Decrease dose by 5 mg/d until total daily dose is 0.3 mg/kg/d	1st mo: 0.3 mg/kg/d 2nd mo: 0.2 mg/kg/d 3rd mo: 0.1 mg/kg/d 4th mo: 0.05 mg/kg/d (or 2.5 mg PO qd)	5th mo: total steroid withdrawal (if no rejection for the past 3 mo)
Calcineurin inhibitors					
Tacrolimus	0.05 mg/kg PO preoperatively; 0.1 mg/kg PO qd in two divided doses; dose target levels 0–1 mo, 10–15	Dose target levels 2–6 mo, 10–12 7–12 mo, 10–12 12+ mo, 8–12			
Cyclosporine	2 mg/kg PO preoperatively; 1 mg/kg IV over 24 h., then 3–5 mg/kg PO qd in two divided doses (based on renal function); dose target levels 0–1 mo, 200–250	Dose target levels 2–6 mo, 150–225 7–12 mo, 125–175 12+ mo, 100–125			
Antimetabolite					
Mycophenolate mofetil	1,000 mg PO preoperatively; 2–3 g IV/PO qd in two divided doses; dosage to keep white blood cell count > 4.0	2–3 g PO qd in two divided doses			
Azathioprine	34 mg/kg PO preoperatively; 3 mg/kg IV/PO qd postoperatively	1–3 mg/kg PO qd			

[a]Data from Refs. [21–25].
IV, intravenously; PO, orally.

General Complications of Heart Transplantation

Right Heart Failure and Pulmonary Hypertension

Frequently acute right heart failure in the postoperative heart transplant patient is secondary to pulmonary hypertension. As mentioned, patient selection is crucial in identifying those recipients with fixed pulmonary hypertension. Those with a pulmonary vascular resistance ≥4 WU, a systolic pulmonary artery pressure ≥60 mm Hg or a transpulmonary gradient ≥15 mm Hg that does not reverse with vasodilator therapy such as inhaled nitric oxide or a prostacyclin analogue such as epoprostenol should not receive a heart transplant. Despite this, there are still recipients who will have some degree of pulmonary hypertension that will cause right heart strain post-transplantation.

Though right heart failure is frequently accompanied by pulmonary hypertension, other causes include donor selection, poor preservation, or prolonged ischemia time. The main principles of management in all cases of right heart failure are to preserve coronary perfusion, optimize RV preload, and reduce afterload by using high inspired oxygen concentrations, inhaled nitric oxide, and prostacyclin [30]. Intravenous milrinone or dobutamine followed later by oral sildenafil are also mainstays

TABLE 183.3

ISHLT CARDIAC BIOPSY GRADING FOR ACUTE CELLULAR REJECTION

Grade	
0R	No rejection
1R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
2R, moderate	Two or more foci of infiltrate with associated myocyte damage
3R	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage, ± vasculitis

ISHLT, International Society for Heart and Lung Transplantation. Data from Stewart S, Winters GL, Fishbein MC, et al: Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 24:1710, 2005.

of therapy. Finally, in severe cases of right heart failure in the acute postoperative setting, a temporary right ventricular assist device is used to bridge the heart to recovery. The need for mechanical assistance typically lasts only a few days to a week and a low threshold should be kept for implanting a device.

Rejection

Surveillance for rejection in the heart transplant recipient by evaluating endomyocardial biopsies of the right ventricle obtained via the right internal jugular vein is performed frequently during the first year and eventually lessens to two to three times per year. There are four types of rejection: hyperacute, acute cellular, acute humoral, and chronic. The grading scale for rejection was recently revised to simplify it and because there appeared to be little clinical difference between grade 1A and 1B rejection in the old classification and also there was evidence of a benign clinical course for grade 2 rejection in the old classification as well [31]. The new grading system is shown in Table 183.3.

The mainstay of treatment is pulse corticosteroids administered intravenously for 3 days, with or without a subsequent taper. In the case of hemodynamically significant rejection or suspected acute humoral rejection, ultrafiltration, and intravenous immunoglobulin are administered to lower circulating antibodies. The addition of methotrexate or cyclophosphamide also should be considered. Photopheresis has been used to treat patients who have preexistent high levels of PRAs [32]. Late chronic rejection manifests as cardiac allograft vasculopathy, is thought to be due to a combination of humoral and cellular rejection, and is the greatest threat to long-term survival. When a patient has no other options to treat chronic, unrelenting rejection, the last resort is retransplantation.

Infection and Pneumonia

Patients who have undergone thoracic organ transplantation are susceptible to bacterial, fungal, and viral infections. The most morbid viral infection that occurs in thoracic organ transplant recipients is caused by cytomegalovirus (CMV) [33]. Transmission of CMV by a donor organ is very common and hence prophylaxis with ganciclovir is used in CMV-mismatched thoracic transplant recipients. Patients who are seronegative at the time of transplantation and receive a graft from a seropositive donor sustain the highest rate of infection and exhibit the most severe form of CMV disease. Ganciclovir is the treatment of choice.

Pulmonary complications occur in approximately a third of heart transplant recipients [33,34] and is the most common infectious complication in heart transplant recipients. In the first 6 months, hospital acquired bacterial pneumonia is the most common pulmonary complication followed by Aspergillus pneumonia. The overall mortality associated with pneumonia is 35% to 55% and accounts for 40% of all cause mortality. A heightened vigilance for pulmonary infection is critical and the presence of yeast- or mold-positive sputum should be aggressively treated. Risk factors for pulmonary complications are older recipient age, moderate to severe rejection, and development of CMV antigenemia in a previously CMV-seronegative recipient [33].

Coronary Allograft Vasculopathy

The development of coronary allograft vasculopathy can lead to myocardial infarction and sudden death in the cardiac transplant recipient. Routine annual coronary angiography with intravascular ultrasound is performed to permit an accurate assessment of the time of onset and rate of progression of coronary artery disease. Graft atherosclerosis occurs in 30% to 40% of transplant recipients after 3 years and in 40% to 60% of patients by 5 years after transplantation [35]. It remains the major obstacle to long-term survival in cardiac transplant recipients. A correlation between CMV infection and accelerated allograft atherosclerosis has also been identified [36]. Immunologically mediated endothelial damage has been proposed as a stimulus for the development of graft atherosclerosis. Treatment can be temporizing in the form of angioplasty for focal lesions; however, when the disease involves tapering of the distal vessels, only cardiac retransplantation can ultimately treat the problem.

Renal Failure

Renal failure in the perioperative period is often transient, and it may be the direct result of nephrotoxic immunosuppressive drugs. Mild impairment of renal function preoperatively is acceptable as long as the risk of severe renal impairment during the postoperative period is recognized as a possible complication. The lowest acceptable level for creatinine clearance in a potential thoracic organ transplant recipient is 50 mL per minute. For suitable patients, combined heart and kidney transplant can be considered. It is also possible for a patient to be listed for a kidney transplant following thoracic organ transplantation.

Posttransplant Lymphoproliferative Disease

Posttransplant lymphoproliferative disease is a common cause of late death following solid-organ transplantation. It is more commonly seen in the pediatric population and is associated with exposure to the Epstein–Barr virus (EBV). Those at greatest risk for posttransplant lymphoproliferative disease are individuals who are EBV-seronegative before transplant who convert after their transplant. Those individuals who are EBV seropositive before transplant are at a lesser risk but are not risk free. Management includes vigilant monitoring of the patient's EBV status, EBV polymerase chain reaction testing, and regular examinations of lymph node beds for enlargement. Therapy once this problem occurs has not been standardized and runs the gamut of antiviral agents, reduction of immunosuppression, anti-CD20 antibodies (such as rituximab), chemotherapy, and radiation therapy. Many of these have been used in combination.

Gastrointestinal Problems

Approximately 40% of patients experience gastrointestinal complications post-transplant. The majority is related to drug side effects, most notably MMF that can cause nausea, vomiting, and diarrhea [37]. These are most often managed with dose adjustments. Serious complications of the alimentary tract following heart and heart–lung transplantation have been well documented and remain a major source of morbidity and mortality [38]. For that reason, patients with active peptic ulcer disease or diverticular disease are not considered for thoracic organ transplantation, at least until these problems have resolved. Mild liver dysfunction as evidenced by elevation of serum transaminase values and hyperbilirubinemia may occur in patients receiving high doses of cyclosporine. This is a chemical hepatitis that usually responds to a decrease in the dosage. Other immunosuppressants such as azathioprine have been implicated in a similar process. Hepatitis may also be secondary to hepatitis B, CMV, herpes simplex virus, hepatitis A, or hepatitis C.

Biliary tract disease is common in the thoracic organ transplant population. In a series of heart transplant recipients, the incidence of cholelithiasis ranged from 30% to 39%, which is more than twice that expected for age- and gender-matched controls [39]. The primary cause of this problem is thought to be gall bladder stasis and the side effects of specific immunosuppressants [40].

Cardiac Retransplantation

Cardiac retransplantation represents a small fraction of the transplants that are performed annually (the UNOS/OPTN database: 3% to 5% annual retransplant rate) [2]. According to the ISHLT database, approximately 2% of all adult heart transplants internationally are retransplants. In the pediatric heart transplant population, this rate is approximately 6% of all transplants. Current 1-year survival for heart retransplant is 82%, closely approaching the 1-year survival of the original transplant [3]. The primary indications for retransplantation appear to be early graft failure, and in later time periods, chronic rejection or graft atherosclerosis.

HEART–LUNG TRANSPLANTATION

Heart–lung transplants are performed almost exclusively in patients with surgically uncorrectable congenital heart disease and Eisenmenger's physiology [41]. Patients with unrelated severe cardiomyopathy and pulmonary disease may also be candidates for heart–lung transplants. With the difficulty of obtaining a heart–lung block and the outcomes of these procedures, many surgeons repair the congenital heart defect and transplant only the lungs [42]. More and more patients with primary pulmonary hypertension are being treated with bilateral single-lung transplant rather than with heart–lung transplant.

There has been a constant decline in the number of heart–lung transplants performed since the mid-1990s, both nationally and internationally, with fewer than 90 heart–lung transplants being performed annually in the current era [2].

Donor Criteria and Organ Procurement

The donor criteria are similar to the criteria used for heart (as listed previously) and lung transplantation (see Chapter 189). The procurement of the heart–lung block entails simultaneous use of techniques that are otherwise used to procure these same organs separately.

Operative Technique: Heart–Lung Transplant

From the outset, the recipient is placed on cardiopulmonary bypass. The recipient heart is excised first, and then each lung is removed. The phrenic neurovascular bundles are protected bilaterally [39]. The left recurrent laryngeal nerve is also at risk for damage in the region of the ligamentum arteriosum. For that reason, some surgeons leave a portion of the main and left pulmonary artery in situ. The tracheal anastomosis is performed first. Although it can be wrapped with omentum, it does not need to be, because the coronary–bronchial collateral circulation is generally excellent. Performance of the right atrial anastomosis or bicaval anastomoses is followed by the aortic anastomosis. Large aortopulmonary collaterals and bronchial vessels can develop in patients with chronic cyanosis and Eisenmenger's physiology. Extreme care must be taken during the operative procedure in these patients to avoid postoperative bleeding.

Postoperative Care

Postoperative care of patients who have had heart–lung transplantation can be quite complex. Potential complications from the heart or the lungs can arise. The standard postoperative care most closely resembles that of a lung transplant patient, and is discussed in a separate chapter. Postoperative bleeding can be quite profound in this subset of patients, even with careful operative control of collateral vessels.

Outcomes

As of 2009, the current registry reports from ISHLT demonstrate a 1-year survival rate of only 75% for individuals undergoing a heart–lung transplant. The average survival for this group who were transplanted between 1982 and 2003 was 3.2 years. Because of the significant mortality rate that occurred within the first year after the transplant, the conditional half-life was higher at 9 years [27]. Early mortalities were due to technical complications, graft failure, and non-CMV infections accounting for 73% of the deaths. Mortality that occurred beyond the first year was attributed to chronic lung rejection with bronchiolitis obliterans, whereas cardiac rejection or coronary vasculopathy played a minimal role.

In the field of heart–lung transplantation, it was initially thought that endomyocardial biopsy would be the appropriate diagnostic test to detect rejection [43,44]. However, with two organ systems involved, the lungs often reject despite normal findings on endomyocardial biopsy [45]. Transbronchial biopsy reveals what is occurring in the lungs during the perioperative period and, later, complications in the lung grafts may be suggested when there are changes on chest radiograph or in pulmonary function studies, and should be evaluated with transbronchial biopsy [46]. Treatment of recurrent lung rejection consists of pulse corticosteroids with or without a taper. Alternate therapies including lympholytic agents, photopheresis, methotrexate, or cyclophosphamide may be used for refractory cases of rejection [47].

CONCLUSION

The discipline of heart transplantation has recently passed its 40th anniversary, and many major advances have been made.

In spite of the changes that have occurred in recipient criteria, the greater number of potential recipients coming to transplant who are more than 60 years of age, on inotropic support, or using mechanical assist, the outcomes of heart transplantation have improved with each passing year. The field has also enjoyed seeing a decrease in candidate waiting times on the list and the evolution of cardiac assist devices to improve candidates for heart transplant. Clearly, knowledge of cardiac transplant is directly related to the duration of experimental and clinical experience. It is expected that, as understanding continues to expand, long-term survival of transplant recipients will increase.

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CHAPTER 184 ■ CARE OF THE PANCREAS TRANSPLANT RECIPIENT

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Type 1 diabetes mellitus has two treatments: (a) exogenous insulin administration or (b) beta cell replacement by pancreas or islet transplantation. The former is burdensome to the patient and gives imperfect glycemic control, predisposing to secondary complications of the eyes, nerves, kidneys, and other systems. The latter, when successful, establishes a constant euglycemic state but requires major surgery—at least for the pancreas transplant—and immunosuppression to prevent rejection, predisposing to complications as well, often compounded by those that are preexisting from diabetes.

The Diabetes Control and Complications Trial [1] showed that intensive insulin therapy (multiple injections per day with doses adjusted by frequent blood sugar determinations) decreased, although rarely normalized, glycosylated hemoglobin levels (HbA1C) and reduced the rate of secondary complications [2]. The threshold for totally eliminating the risks of secondary diabetic complications was perfect glycemic control, an objective that cannot be achieved by even the most sophisticated exogenous insulin-delivery devices available today. Pancreas transplantation induces insulin independence in diabetic recipients without the risk of hypoglycemia and can ameliorate secondary complications. With major advances in the area of management of pancreas transplantation (Table 184.1), the success rate has progressively increased during the past five decades [3]. Today's recipients have a high probability of achieving insulin independence for years, if not indefinitely.

Historically, islet transplants have been less successful than pancreas transplants for a variety of reasons, but the gap is narrowing. In the late 1990s at the University of Alberta, insulin independence was achieved by sequential transplantation of islets from multiple donors and the use of a steroid-free, nondiabetogenic, immunosuppressive regimen [4]. In another series from the University of Minnesota with a similar immunosuppressive regimen, single-donor islet transplants induced insulin independence [5]. In this series, the donors had a high body mass index and the recipients had a low body mass index, so that the net number of islets transplanted per unit weight was similar in the Alberta and Minnesota series. Islet transplants can succeed with strict donor and recipient selection, but are not yet able to supersede pancreas transplants as the mainstay of beta cell replacement. Until islet transplants can consistently succeed from a single donor, regardless of recipient size or insulin requirements, an integrated approach is likely; large donors will be used for islet transplants to recipients with low insulin needs and the remaining donors (the majority) for pancreas transplants to recipients with average- or high-insulin requirements. This strategy will maximize the number of recipients who receive allogeneic beta cells and eliminate surgical complications for at least a subset of patients.

Although short-term islet-graft survival appears promising (even with single donors) [6], long-term graft function after islet transplants (even with multiple donors) continues to be a major impediment to rapid progress. In the University of Alberta series, only 10% of islet transplant recipients were insulin independent at 5 years posttransplant [7].

The main trade-off for recipients of beta cell allografts is the need for immunosuppression. A successful graft makes the recipient euglycemic and normalizes glycosylated hemoglobin levels, but the combined risks of immunosuppression and a major pancreas transplant surgery must be weighed against the long-term risks of imperfect glycemic control with exogenous insulin injection and of development of secondary complications. A randomized prospective trial has not been done to weigh these risks. The burden of daily management of diabetes with the need for multiple sticks to monitor blood sugar levels and to inject insulin tilts the balance in favor of a pancreas or islet transplant for many diabetic patients. Furthermore, antirejection strategies are continually being modified to decrease the complications of immunosuppression. Nevertheless, only a few institutions perform pancreas transplants soon after the onset of diabetic disease [8]; most institutions delay pancreas transplantation until the recipient becomes uremic and needs a kidney transplant.

The main indications for pancreas transplants in patients with normal kidney function are progressive diabetic complications, glycemic lability, and hypoglycemic unawareness, the latter of which may emerge years after the onset of diabetes, particularly in patients with autonomic neuropathy. However, even for nonlabile diabetic patients who attempt tight control by intensive glucose monitoring, the diabetes literature shows a high rate of secondary complications that are just as morbid [9] as complications of chronic immunosuppression in pancreas transplant recipients. Thus, for patients who wish to avoid a lifetime of insulin injections and glucose monitoring and prefer the risks of immunosuppressive complications to the secondary complications of diabetes, a pancreas transplant can be an attractive alternative therapy.

Most pancreas transplant candidates have advanced diabetic nephropathy and require a kidney transplant also. The risks of immunosuppression are already assumed because of the kidney transplant, so a simultaneous or sequential pancreas transplant does not pose significant additional risks other than surgical ones [8]. Although most pancreas transplants are performed in type 1 diabetics with impending or chronic renal failure, some pancreas transplants occur in renal allograft recipients who meet the criteria for type 2 diabetes who want to eliminate the need for exogenous insulin [10].

PANCREAS TRANSPLANT RECIPIENT CATEGORIES

Pancreas transplant candidates are divided into three categories: uremic (need a kidney transplant), posturemic (have a functioning kidney transplant), and nonuremic (do not need a kidney transplant, at least yet). For candidates who are

TABLE 184.1

MAJOR ADVANCES IN THE MANAGEMENT OF PANCREAS TRANSPLANTATION

Topic	Change	References
Organ donation	1) Increased donor pool due to use of organs from donors after cardiac death with comparable graft survival rates to recipients of organs from brain-dead donors 2) Greater application of the expanded donor for pancreas organs	[50,84–90]
Preservation fluids	Improved pancreas preservation fluids/techniques	[92–115]
Pancreas transplant operation	1) Shift from bladder to enteric drainage of pancreatic exocrine secretions 2) Shift from systemic to portal venous drainage 3) Shift toward deceased pancreas transplant after living kidney transplant 4) Increased application of islet cell transplant 5) Increased laparoscopic living donor kidney and segmental pancreas organ procurement	[11,13,14,37,40, 85,124–137]
Immunosuppressive regimens	1) Tacrolimus and mycophenolate mofetil have replaced cyclosporine and azathioprine with improved graft survival 2) Increased use of depleting antibody to encourage innovative immunosuppressive strategies (steroid withdrawal or avoidance, calcineurin withdrawal, monotherapy)	[132–138]

uremic, the options are to receive kidney and pancreas transplants either simultaneously in the same operation or sequentially in separate operations. Which option to take is usually based on the availability and suitability of living and deceased donors for one or both organs at that particular time.

Accordingly, there are three broad categories of pancreas transplants: simultaneous pancreas kidney (SPK) transplant, pancreas after kidney (PAK) transplant, and pancreas transplant alone (PTA).

1. SPK transplants: Most SPK transplants are performed with both organs from the same deceased donor. Because a large number of patients wait on the UNOS list for a kidney organ, unless priority is given to SPK candidates, waiting times tend to be long (years). To avoid two operations and long waiting times, a simultaneous kidney and segmental pancreas transplant from a living donor can be done, but only a few centers offer this option. With successful islet transplantation from a living donor [11], a simultaneous living donor islet-kidney transplant may become a viable option in the future. If a living donor is willing or is medically suitable to give a kidney organ only, another option is a simultaneous living donor kidney and deceased donor pancreas transplant [12]. For this option, the living kidney donor and the recipient must be available at a moment's notice, because the deceased donor pancreas must be transplanted soon after procurement. Alternatively, a recipient of a scheduled living donor kidney transplant could receive a simultaneous deceased donor pancreas organ if it became available fortuitously. If not, and only a living donor kidney is transplanted, the recipient becomes a PAK candidate.
2. PAK transplants: For diabetic patients who have already received a kidney transplant from a living or deceased donor, a PAK transplant can be performed. Most PAK transplants today are performed from a deceased donor in a patient who previously received a living kidney transplant. Although a PAK transplant requires that a uremic diabetic patient undergoes two operations to achieve both a dialysis-free and insulin-independent state, the two transplants done separately are "smaller" procedures than a combined transplant. The time interval between the living donor kidney transplant and the deceased donor pancreas transplant depends on several factors, including recipient recovery from the kidney transplant and donor availability, but the outcomes are similar for all time intervals greater than 1 month duration. Because of the lack of priority of patients who wait for a SPK versus a kidney alone, the PAK is now becoming the most popular pancreas transplant category at many institutions [13,14].
3. PTA: For recipients with adequate kidney function, a solitary pancreas transplant can be performed from either a living or deceased donor. Because the waiting time for a solitary deceased pancreas is relatively short at the present time, living donor solitary pancreas transplants are done infrequently, but are typically indicated if a candidate has a high panel-reactive antibody and a negative cross-match to a living donor. PTA candidates have problems with glycemic control, hypoglycemic unawareness, and frequent insulin reactions but fairly normal renal function. A successful PTA not only obviates these problems, but also probably improves the quality of life, and may ameliorate secondary diabetic complications, thus increasing the applicability of PTA [13–15].

Although the numbers of SPK transplants have remained fairly constant for nearly two decades, the numbers of solitary pancreas transplants (PAK and PTA) have nearly quadrupled [16]. From 2004 to 2008, the most common category of pancreas transplant was the SPK (73%), followed by the PAK (19%) and the PTA (9%); in the PAK category, 76% of the kidney organs came from living donors [3]. Although rare, pancreas transplants can also occur as multiorgan transplants in patients with unique medical problems [17].

HISTORICAL PERSPECTIVES, EVOLUTION, AND IMPROVEMENTS IN PANCREAS TRANSPLANTS

The first clinical pancreas transplant was performed at the University of Minnesota in 1966 [18]. The number of transplants remained low during the 1970s, but progressively increased in the 1980s, due to the introduction of cyclosporine.

By the end of 2008, more than 30,000 pancreas transplants were reported to the International Pancreas Transplant Registry (IPTR) from more than 1,000 centers worldwide, including more that 22,000 in the United States and more than 8,000 outside the United States [3]. In 2010 more than 3,700 patients wait for a pancreas transplant on the UNOS list, and more than 1,200 pancreas transplants have been done annually in the United States [17].

The early history of pancreas transplants involved various surgical techniques, many of which were developed to manage pancreatic exocrine drainage [19]. The first clinical pancreas transplant was performed by Kelly et al. as a duct-ligated, segmental graft at the University of Minnesota in December 1966 [18,20]. In 1973, Lillehei described a series of 13 pancreas transplants at the University of Minnesota where he used enteric drainage (ED) of pancreatic secretions via a cutaneous duodenostomy and a roux-en-y-duodenojejunostomy [20,21]. In the 1970s, Gliedman reported the first segmental pancreas transplant (and then a series of 11 pancreas transplants) with a pancreatic duct–ureter anastomosis for exocrine drainage [20–23]. This technique did not have widespread popularity because of leakage from the pancreatic duct–ureter anastomosis and the cut surface of the pancreas [20].

From the mid-1970s to mid-1980s, segmental pancreas transplants predominated due to a historical belief that the pancreas organ was less antigenic than the duodenal stump [20,21]. With segmental pancreas transplants, two techniques were popularized to manage pancreatic exocrine secretion, including open intraperitoneal drainage by Bewick in 1976 and the University of Minnesota in 1978 [20,24] and synthetic polymer pancreatic duct injection by Dubernard in 1978 [20,25]. In 1983, Sollinger reported the use of direct bladder drainage (BD) to manage pancreatic exocrine secretions in a segmental pancreas graft [26], and the next year he described a series of 10 segmental pancreas transplants with BD that had very few surgical complications, so BD became the predominant technique (Fig. 184.1) [20,27]. In 1982, Groth and Tyden described a segmental pancreas transplant followed by a series of whole-organ pancreas transplants with ED (Fig. 184.2) [28] and this technique ended the predominance of segmental pancreas transplants [20,29].

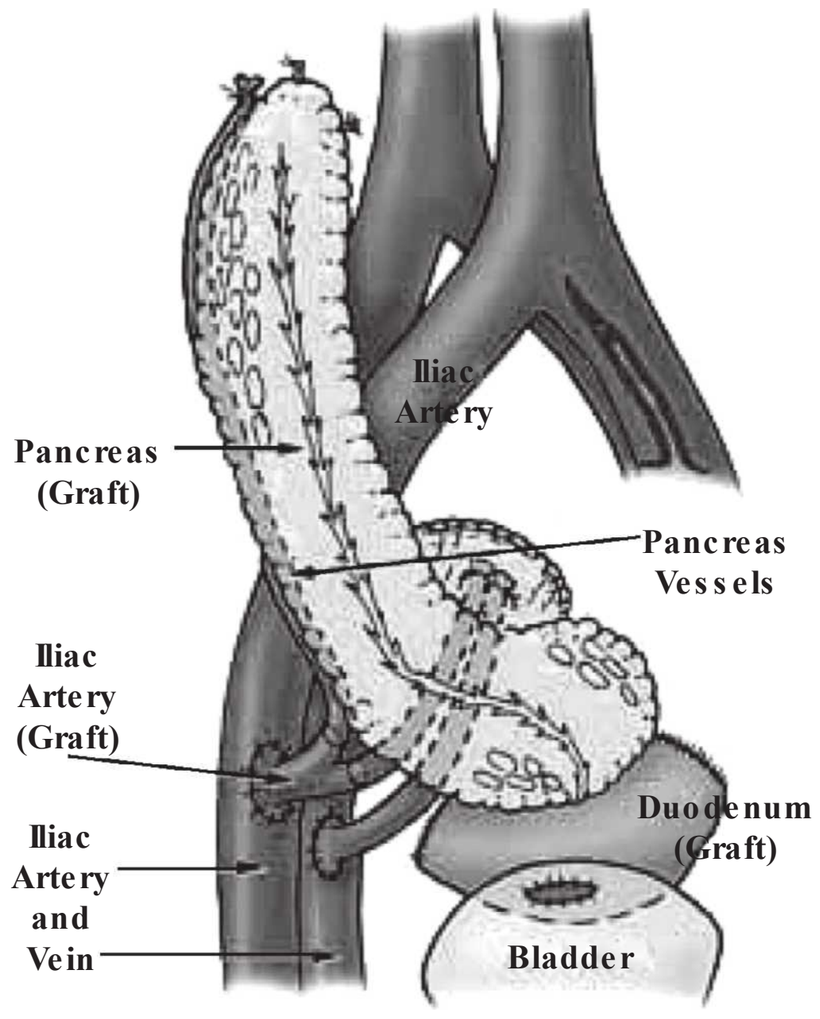

FIGURE 184.1. Bladder-drained pancreaticoduodenal transplant alone from a cadaveric donor.

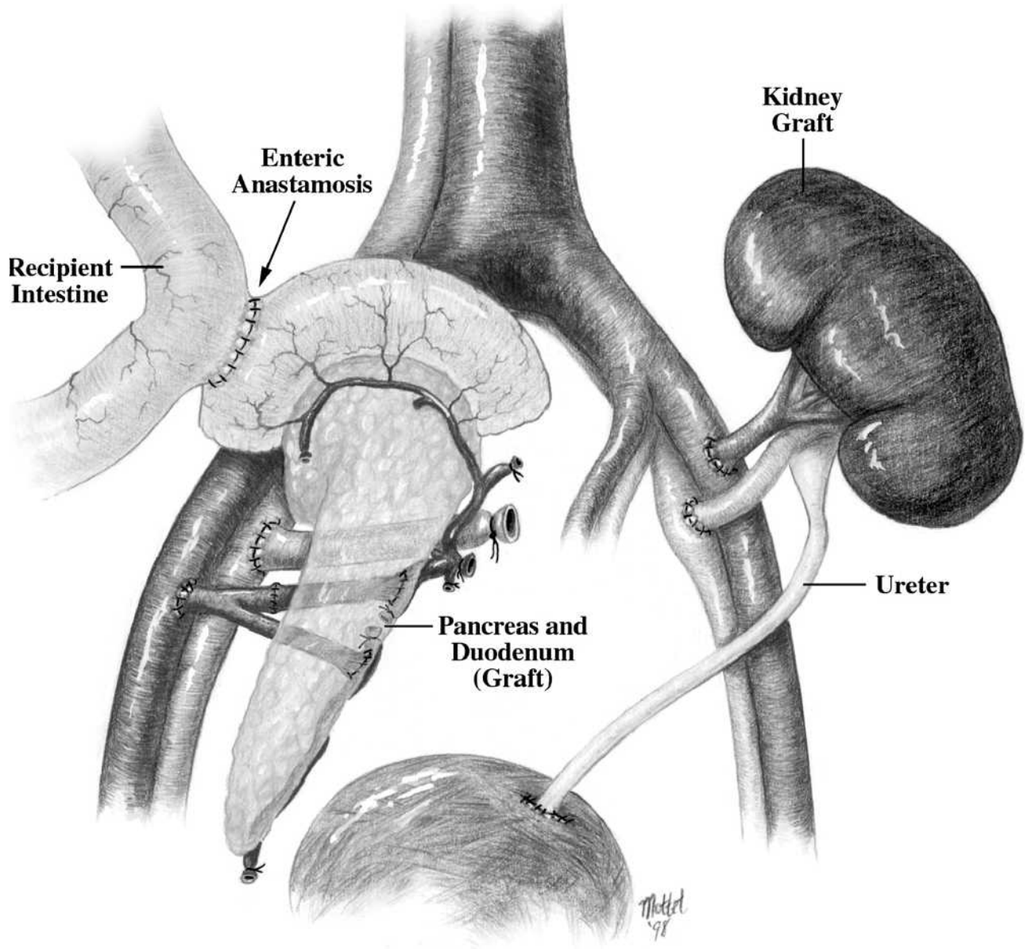

FIGURE 184.2. Enteric-drained simultaneous pancreas and kidney transplant from a cadaveric donor with systemic venous drainage.

In 1987, Nghiem et al. described a whole-organ pancreas transplant with BD via a duodenal stump, a technique that took on widespread acceptance in both Europe and the United States. BD was especially appealing because urinary amylase levels could be tracked to monitor rejection and pancreatitis [20,30]. In mid-1980s, Starzl revived ED of the whole-organ pancreas transplant described by Lellehei 20 years previously [20,31]. In the mid-1980s to the mid-1990s, although BD was popular, urinary complications including cystitis, urethritis, hematuria, metabolic acidosis, and volume depletion led to enteric conversion of whole-organ pancreas transplants in a technique first described by Tom in 1987 [20,32].

Venous drainage of the pancreas has also evolved over the years. Portal drainage was used with segmental grafts in the 1980s [33–36]. In 1989, Mühlbacher described the first case of whole-organ pancreas transplantation with portal venous drainage and exocrine BD [37]. Until 1990s systemic venous drainage had been the norm, until portal drainage gained widespread popularity with ED [38,39] as opposed to BD [37]. By 2004, about 20% of SPK transplants had portal drainage, most commonly to the superior mesenteric vein (Fig. 184.3) and 80% of SPK had ED of pancreatic exocrine secretions [40].

Before standard techniques were developed to procure liver and pancreas grafts with intact blood supplies, segmental pancreas grafts were commonly used. Currently, whole-organ pancreaticoduodenal grafts predominate, although segmental grafts are still used for living donor pancreas transplants. The first living donor pancreas transplant was performed at the University of Minnesota in 1979 [41]. The early series of living donor pancreas transplants consisted of solitary pancreata because the rejection rates for deceased donor pancreata were so high [42]. In the 1990s, living donor pancreas transplants were predominantly performed in combination with a kidney from the same donor (Fig. 184.4) [43–45]. More recently, laparoscopic living donor segmental pancreatectomy has gained popularity [46]. Another approach, as previously mentioned, is to perform a living donor kidney transplant simultaneously with a deceased donor pancreas transplant [12].

Immunosuppressive regimens have made great strides over the years. Most immunosuppressive protocols use antibody

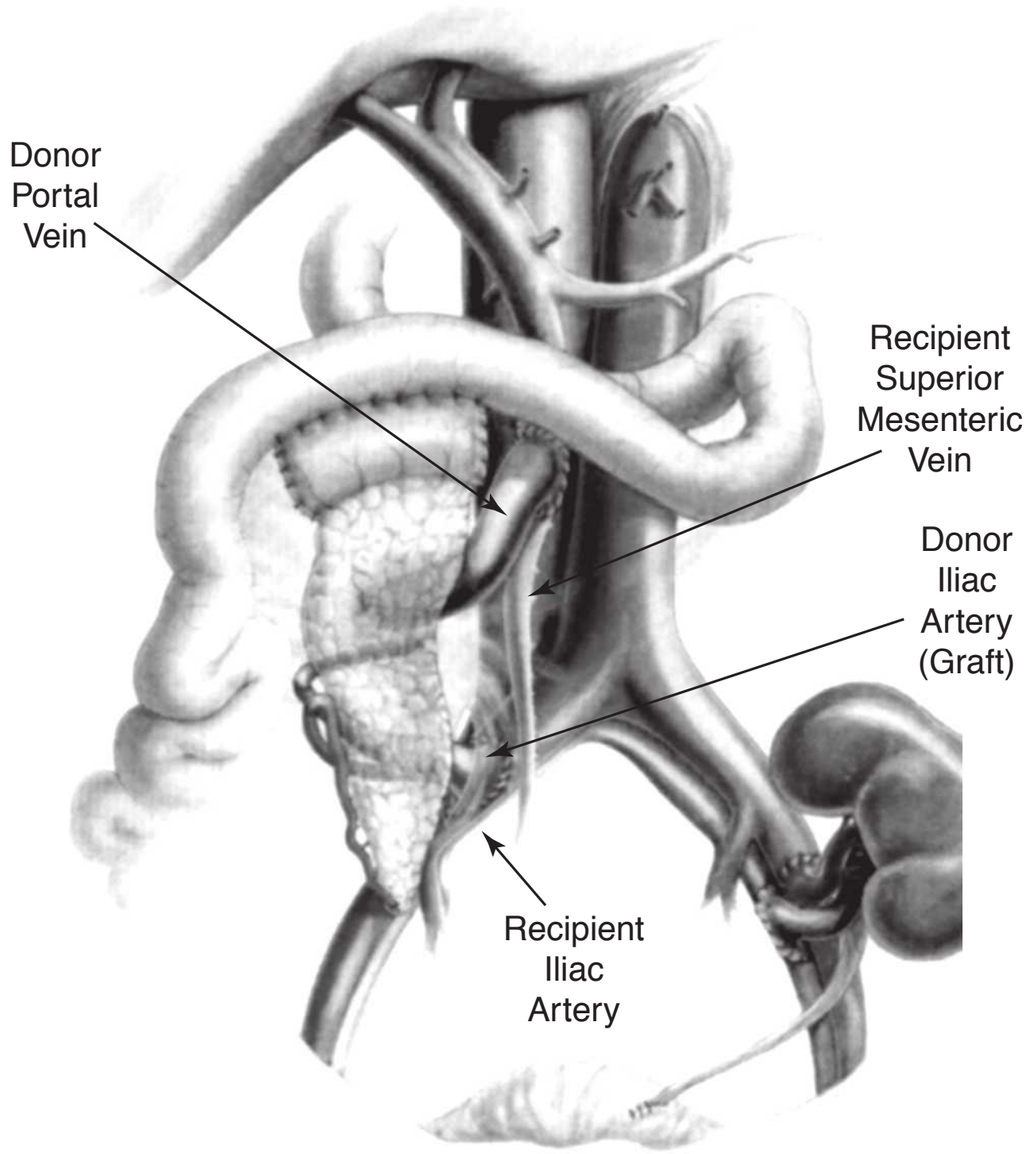

FIGURE 184.3. Enteric-drained simultaneous pancreas and kidney transplants with portal venous drainage of the pancreas graft via the superior mesenteric vein.

induction, followed by maintenance therapy with tacrolimus in combination with mycophenolate mofetil [40]. In the late 1990s and early 2000s some centers such as Northwestern University pushed for steroid-free regimens for pancreas transplants [20]; in fact, of the nearly 25,000 pancreas transplants reported to the IPTR, a third of those in the last 5 years were done with a steroid-free immunosuppressive regimen [20,40]. Today there are more than 140 pancreas transplant centers and 25 islet cell transplant centers in the United States [17]. Some centers have reported extensive experience, including more than 1,000 SPK transplants at the University of

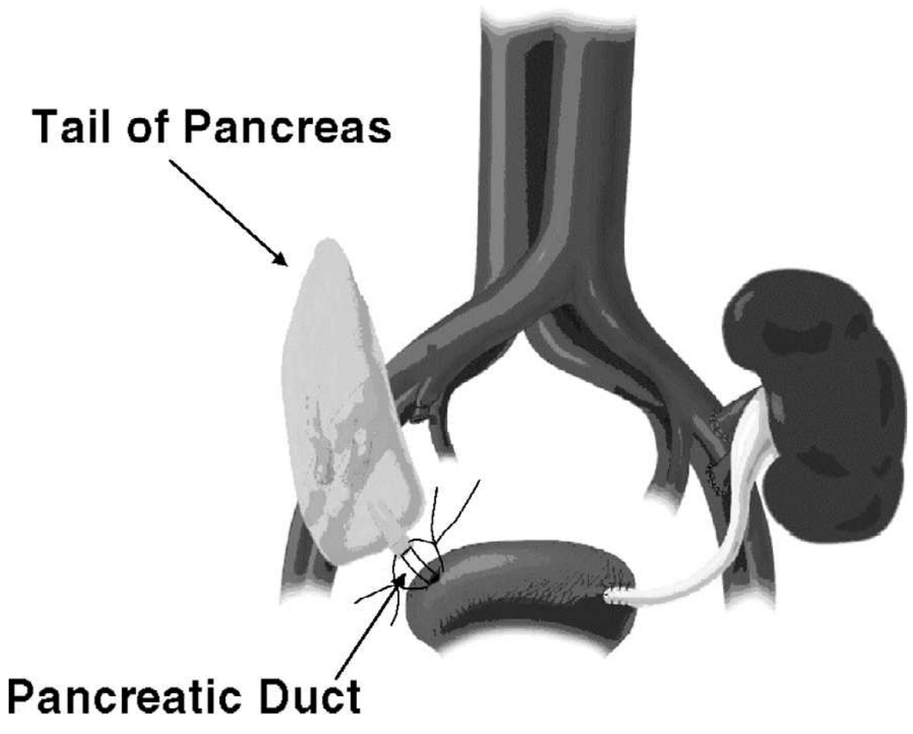

FIGURE 184.4. Simultaneous segmental pancreas and kidney transplant from a living donor. Either bladder- or enteric-drained can be used, but the bladder-drained technique has a lower complication rate and is illustrated.

TABLE 184.2

SUMMARY OF AMERICAN DIABETES ASSOCIATION RECOMMENDATIONS FOR INDICATIONS FOR PANCREAS TRANSPLANTS

Indication for pancreas transplants
1). Imminent or established end-stage renal disease in patients who have had, or plan to have, a kidney transplant
2). History of frequent, acute, and severe metabolic complications (e.g., hypoglycemia, hyperglycemia, ketoacidosis)
3). Incapacitating clinical and emotional problems with exogenous insulin therapy
4). Consistent failure of insulin-based management to prevent acute complications
5). Islet cell transplants hold significant potential advantages over whole-gland transplants but the procedure is experimental and should be performed only within the setting of controlled research studies

Wisconsin [17], and more than 1,900 pancreas transplants of all categories at the University of Minnesota [17]. Since 1980, the IPTR has collected data from all centers in the world [47] and remains an excellent resource for outcome analysis. In addition, the US Transplant Scientific Registry of Transplant Recipients (SRTR), administered through the Arbor Research Collaborative for Health, provides detailed scientific analysis of national, regional, state, and center-specific pancreas graft and patient survival [48].

INDICATIONS AND CONTRAINDICATIONS FOR PANCREAS TRANSPLANTS

The indications for a pancreas transplant have evolved and expanded over the years as the results have improved. The position statement of the American Diabetes Association [49] on indications for a pancreas transplant (Table 184.2) is fairly conservative. A pancreas transplant is also indicated for patients who have developed secondary complications of diabetes including retinopathy, cardiovascular disease, nephropathy, and neuropathy. The progression of many of these complications is halted by a functioning pancreas graft.

With a functioning pancreas transplant improvements with sensory, motor, and autonomic neuropathy and paresthesias have been reported [19,50–55]. Patients with abnormal cardiorespiratory neurologic reflexes have reduced death rates after functioning pancreas transplants [50,56]. There is increased nerve conduction velocity in SPK recipients with functioning pancreas transplants versus those with failed pancreas grafts [51,57,58]. Uremic patients who undergo SPK transplants have improved symptoms of gastroparesis than in patients who have kidney transplants alone [52,59].

Similarly a successful pancreas transplant halts the progression of diabetic changes in the new kidney transplant, and several studies have demonstrated improvement of nephropathy after PTA [50–52]. One study showed that long-term normoglycemia due to a functioning pancreas transplant led to reversal of characteristic diabetic glomerular lesions that occurred in nonuremic PTA recipients who had established nephropathy [52,60]. In addition to improvement in glomerular architecture, this group also showed a reversibility of cortical

interstitial expansion and reabsorption of atrophic renal tubules 10 years after PTA [52,61]. These changes in renal architecture may explain the reduction in blood pressure, albuminuria, and nephrotic range proteinuria that some PTA recipients demonstrate [52,62,63], but creatinine clearance can still deteriorate.

Several recent reports have shown stabilization or amelioration of diabetic retinopathy with a functioning pancreas transplant [50–52]. Ramsey et al. reported reduced deterioration in advanced retinopathy with a functioning pancreas transplant at 3 years [52,64]. Wang et al. reported regression of diabetic retinopathy in 43% of SPK recipients versus 23% of kidney transplant alone recipients, although nearly 50% of both groups showed no benefit but follow up was short at 1 year [50,65]. Giannarelli et al. examined 33 type 1 patients who received a pancreas transplant versus 36 type 1 patients who had medical therapy only, and noted that stabilization or amelioration of diabetic retinopathy was 91% versus 43%, respectively [51,66].

Several studies have examined the effects of pancreas transplantation on vasculopathy and cardiovascular risk factors. Severe and advanced vascular disease may be unaffected by a functioning pancreas transplant [50,51]. One series documented improvement in conjunctival microcirculation in 12 SPK patients when compared with five kidney transplant alone recipients [52,67], and other series reported improvement in carotid artery intima-media thickness (which correlates with decreased cardiovascular events) within 2 years of pancreas transplantation [50,52,68,69]. SPK transplants have also shown to improve cardiovascular risk factor profiles, progression of coronary atherosclerotic lesions, left ventricular systolic and diastolic function, and endothelial function [50–52,70–76]. Atherosclerosis regresses in nearly 40% of recipients with a functioning pancreas transplant and this fact may explain improved quality of life and patient survival benefit after pancreas transplantation [50,51,70]. Fiorina et al. demonstrated normalization of left ventricular diastolic function at 4 years after a functioning pancreas graft [50,51,77], which leads to reduction in cardiovascular events [74]. Rates of myocardial infarction and pulmonary edema were lower in SPK recipients than in kidney transplant alone patients, although the kidney alone patients tended to be quite older and the follow up period was short [50,78–80]. Echocardiographic findings 2 years after pancreatic transplantation showed improvement in left ventricular shape and function when compared with kidney transplantation alone. Stabilization [50,56] and even improvement [50,81] in cardiac autonomic dysfunction can occur after pancreas transplantation. A pancreas transplant should really be offered early, before the onset of these complications of diabetes, to interested patients who understand the risks of a significant operation and immunosuppression versus the benefit of insulin independence and freedom from diabetic complications.

Although the most subjective outcome after pancreas transplantation, improved quality of life may be the most important [52]. One study compared the quality of life of diabetic patients who underwent SPK transplants with a kidney transplants alone, and noted that SPK recipients reported improved quality of life in regard to chronic symptoms, effects of kidney disease, cognitive function, pain, physical activity and overall health [82]. Data regarding quality of life in PTA recipients is lacking.

Relative and absolute contraindications include those for any other transplant, such as extremes of age, prohibitive cardiovascular and pulmonary risk, severe hepatic disease, malignancy, active acute and chronic infections, AIDS, severe persistent coagulation disorder, noncompliance, and serious psychosocial problems. Candidates with advanced vascular disease have increased risks of surgical complications, yet, those patients who do well after pancreas transplantation, greatly benefit from stabilization of their cardiovascular risk.

PRETRANSPLANT EVALUATION

The pretransplant workup should include a detailed medical, surgical, and psychosocial evaluation. Cardiac risk assessment is mandatory because diabetes is a major risk factor for coronary artery disease (CAD). Cardiologists vary on the type of test to screen for CAD in pretransplant diabetic patients. Coronary angiograms are performed in most candidates, especially those over 45 years of age. Noninvasive tests are not very sensitive for CAD and are poorly predictive for subsequent postoperative events in long-standing diabetic patients. With the use of iso-osmolar radiographic contrast, there does not seem to be an increased risk of contrast-induced nephropathy in patients with chronic kidney disease [83]. In selected patients (i.e., young, healthy patients with short-duration diabetes) dobutamine stress echocardiograms are used for cardiac evaluation with acceptable results. Once significant CAD is detected, aggressive treatment by angioplasty, stenting, or revascularization is recommended. Revascularized transplant candidates have significantly fewer postoperative cardiac events, as compared with those who received medical therapy alone. The minimum cardiac evaluation should include an ECG, chest radiograph, echocardiogram, and cardiac stress test [50].

A detailed examination must be done to rule out vascular insufficiency in the lower extremities. If such vascular insufficiency is found, it too may need pretransplant correction with angioplasty, endarterectomy, or revascularization, because the transplant operation, often involving an anastomosis to the iliac artery, may further diminish lower extremity blood flow.

Pulmonary function tests are indicated in chronic smokers and patients with a history of chronic pulmonary disease. Postoperative intensive care unit monitoring and perioperative bronchodilator therapy may be indicated in some patients. Liver function tests should be done to rule out hepatic insufficiency and viral hepatitis. The diagnosis of viral hepatitis (especially hepatitis C) is associated with worse long-term outcome after extrahepatic transplantation. Abnormal liver function tests or the diagnosis of viral hepatitis should be followed up with a liver biopsy to rule out cirrhosis. The presence of cirrhosis is a contraindication for pancreas transplant (unless the patient is a candidate for a rare multiorgan transplant). A gastrointestinal evaluation must be done to rule out autonomic dysfunction. Significant symptoms of gastroparesis would prompt a gastric emptying study. Some immunosuppressive medications may worsen gastrointestinal dysfunction (mycophenolate mofetil can have significant gastrointestinal side effects). A prokinetic agent may be indicated to treat gastroparesis. A urologic examination is especially important for bladder-drained recipients because bladder dysfunction predisposes to graft pancreatitis.

CADAVERIC DONOR SELECTION

Pancreas donor selection criteria are not standardized, but instead vary from center to center. Absolute contraindications are the obvious ones applied to most solid organs: active hepatitis

B, hepatitis C (unless the recipient has hepatitis C), human immunodeficiency virus, non-CNS malignancy, surgical or traumatic damage to the pancreas, duodenum or spleen, history of diabetes mellitus, pancreatitis, and extremes of age (less than 10 or more than 60 years). Prolonged intensive care unit stay and duration of brain death have been associated with an increased risk of pancreas graft failure [84]. Other studies have shown that donor age is important. Even middle-aged donors (> 45 years old) are associated with pancreas graft failure and increased complications [85–87]. Small donors (< 28 kg) have been used for pancreas transplantation with good outcomes [88]. Obesity in the deceased donor is a common cause for refusal of solid-organ pancreas donation, and donors with a BMI > 35 kg per m^2 are virtually never used for solid-organ pancreas transplants [50]. Older and obese donors (> 50 years old and > 30 kg per m^2) are probably more suitable for islet cell than for solid-organ pancreas transplantation [50]. Donors after cardiac death are being used increasingly to expand the donor pool. One survey showed equivalent patient and graft survival at 1, 3, and 5 years in SPK transplant recipients from donors after cardiac death compared with ideal donors after brain death [89]. In general, a pancreas from a so-called marginal donor is associated with good outcome if the pancreas is found to be normal on gross inspection [89,90].

In nearly 3,200 consecutive pancreas donors procured between 2000 and 2005 Vinkers et al. determined the influence of a "preprocurement pancreas suitability" score on the acceptance or refusal of deceased pancreas organs [91]. The investigators assigned a weight for several pre-procurement factors including age, BMI, length of ICU stay, cardiac arrest as cause of death, serum sodium, amylase and lipase levels, and need for vasopressor support to develop a donor score. When the donor score was ≥ 17, pancreata from these deceased donors were three times more likely to be refused by transplant centers. Donor scoring systems such as this one may provide more objective information about the quality of a deceased pancreas organ to promote wider pancreas donor acceptance.

Pancreas Preservation

University of Wisconsin solution was first used for pancreas preservation in a preclinical model in 1987 [92]. As with most solid organs, in vivo flush followed by simple storage in cold University of Wisconsin solution is still the gold standard for pancreas preservation. In the original canine model, pancreata were preserved for up to 96 hours [93], but in clinical transplantation, pancreas cold preservation exceeding 24 hours has been associated with increased graft dysfunction. Even less than 24 hours, it is evident that the longer the cold ischemia time, the greater the technical complication rate. Therefore, every effort should be made to minimize the cold ischemia time to optimize graft function and to minimize complication rates. The two-layer method (TLM) using University of Wisconsin solution and perfluorochemical [94] has been used in clinical whole pancreas transplantation but more commonly for islet preservation. This method improves pancreas oxygenation, allowing for longer preservation time while providing a mechanism for repair of ischemic damage due to cold storage [95–97]. Some studies show that TLM improves islet yields, islet viability, islet morphology, rates of successful islet isolations and transplants, and islet yields from marginal donors [97–104]. Other studies report that TLM has no effect or is even detrimental for pancreas preservation, and show no difference in islet yields, islet viability or islet transplant outcomes when pancreas organs were preserved with the TLM versus University of Wisconsin solution [97,98,105,106]. More prospective, randomized, controlled trials are needed before the TLM becomes routine procedure.

Three main preservation solutions for pancreas transplantation are available today, including University of Wisconsin solution, Celsior, and histidine–tryptophan–ketoglutarate solution (HTK) [97,98]. HTK has been increasingly used in pancreas transplantation, and its advantages include lower viscosity, less potassium, lower cost and no need for "on-shelf" cold storage, but it requires more solution to flush organs in the multiorgan donor (8 to 12 L of HTK solution vs. 4 to 6 L of Celsior vs. 4 to 6 L of University of Wisconsin solution) [97]. In pancreas transplantation, there have been only one retrospective study [107] and two prospective randomized studies [108,109], which compare University of Wisconsin solution with Celsior and both solutions give similar results. Several reports [110–114] have compared HTK with University of Wisconsin solution and most reports have described equal suitability for perfusion and organ preservation in clinical pancreas transplantation. In an analysis of the UNOS pancreas transplant database from 2004 to 2008, Stewart et al. [115] noted that HTK preservation was associated with a 1.5-fold higher odds of early (< 30 days) pancreas graft loss when compared with University of Wisconsin solution, and was independently associated with increased pancreas graft loss in SPK and PTA recipients, especially when cold ischemia times were ≥ 12 hours. Further prospective, randomized studies will be necessary to determine which perfusion and preservation solution provides the best short-term and long-term pancreas graft survival.

HLA Matching

The impact of HLA matching on outcome varies. HLA matching appears to have little effect on patient, kidney, or pancreas graft survival after SPK transplantation, [116,117], although increased acute rejection rates have been reported with poorer matches [118–120]. For PAK and PTA transplants the data are mixed, ranging from studies showing no impact [121] to registry data showing that higher HLA A and B mismatches are associated with increased immunologic graft loss [117]. Pancreata have been successfully transplanted across rare positive T cell cross-matches, and intravenous immunoglobulin and plasmapheresis have been used to neutralize or eliminate the antibody [50]. A positive T cell cross-match is much more of a risk for immunologic graft loss than is a positive B cell cross-match (especially in a primary pancreas transplant recipient) [50,122].

Anesthetic Considerations in Recipient

A patient with brittle diabetes and secondary complications (e.g., CAD, autonomic neuropathy) can pose special problems for the anesthesiologist. Dysautonomic response to drugs or hypoxia can lead to significant morbidity and even death. It is well documented that long-standing diabetes poses a challenge to the anesthesiologist during intubation. Awareness of these risks and use of an experienced anesthesiology team might help decrease the morbidity and mortality. A major operation such as a pancreas transplant or combined kidney-pancreas transplant is often prolonged and can be associated with significant blood loss. Prompt replacement with blood or colloid solutions should be instituted to avoid hypoperfusion after significant blood loss, because pancreas hypoperfusion can lead

to thrombosis. In the intra- and peri-operative period, careful blood glucose monitoring is essential, and continuous intravenous (IV) insulin therapy may be necessary to maintain tight control of blood glucose levels. Blood glucose levels may be high in the immediate postoperative period due to high dose steroids, so continuous IV insulin therapy may be required to control hyperglycemia. Perioperative beta-blockade should be considered for long-standing diabetic patients with a cardiac history.

BACK TABLE PREPARATION OF THE DONOR PANCREAS

Back table preparation of the pancreas organ is necessary before implantation, including these steps:

1. Donor splenectomy (taking care to avoid injury to the pancreatic tail)
2. Shortening the donor duodenum without damage to the main or accessory pancreatic duct (especially important with BD to minimize bicarbonate loss)
3. Ligation of the mesocolic and mesenteric stumps on the anterior aspect of the pancreas
4. Excision of excessive lymphatic and ganglionic tissue in the periportal area
5. Reconstruction of the splenic and superior mesenteric arteries with a donor Y graft including the iliac artery bifurcation (to provide for a single-arterial anastomosis in the recipient)
6. Some mobilization of the portal vein
7. Ligation of the bile duct stump

RECIPIENT OPERATION

Several techniques have been described for the recipient operation [123]. The techniques vary based on whether a solitary pancreas transplant (PTA, PAK) or a combined transplant (SPK) is done. Most SPK transplants are performed through a midline intra-abdominal approach although some are performed through bilateral iliac retroperitoneal incisions.

The major surgical considerations for pancreas transplants include the following:

1. Choice of exocrine secretion of the pancreas, ED versus BD: The 2004 IPTR noted that 81% of SPK, 67% of PAK, and 56% of PTA transplants had ED of pancreatic exocrine secretions [40]. ED is much more physiologic and eliminates the complications of BD (e.g., acidosis, pancreatitis, urinary tract infections, hematuria, urethritis, urinary stricture, urinary disruption). Between 10% and 20% of BD recipients ultimately undergo enteric conversion at 6 to 12 months because of such complications. BD, however, allows for direct measurement of urinary amylase as a marker of exocrine function. A decrease in urinary amylase is sensitive, but not very specific, for acute rejection of the pancreas [40]. Hyperglycemia is a late event in rejection, and a decrease in urinary amylase occurs early in rejection. Thus, rejection episodes may be detected earlier with BD than with ED.

   In clinical practice, the choice of exocrine drainage varies. Some groups always use ED, some always use BD, and others determine the choice of exocrine drainage based on the individual recipient's anatomic constraints and the risk of bowel/urologic complications. Patient and graft survival are similar with both techniques [85,124], but BD is associated with higher rates of urinary tract infections, in addition to urologic and metabolic complications [125,126]. ED is likely to predominate as the major technique in the future, as immunologic strategies to eliminate rejection are further refined. ED usually occurs as an anastomosis between the donor duodenal stump and the recipient proximal jejunum, but graft placement behind the right colon can allow for direct duodenoduodenostomy [125,127].
2. Choice of venous drainage, portal or systemic: The 2004 IPTR reported that in enteric-drained pancreas transplants, 20% of SPK, 23% of PAK, and 35% of PTA cases had venous drainage to the portal vein [40]. Portal drainage is more physiologic than systemic drainage. Theoretically, portal drainage preserves the first-pass metabolism of insulin in the liver. Therefore, pancreas recipients with portal venous drainage will have lower systemic insulin levels than recipients with systemic venous drainage. In one study [128] that compared portal with systemic venous drainage in SPK recipients, there were no significant differences in patient, kidney or pancreas allograft survival rates or early graft loss by pancreatitis or thrombosis. There were no significant differences in early endocrine function, although HbA1C was lower at 6 and 12 months in the portal-drained group.

   Portal venous drainage is difficult to perform with BD unless there is a venous extension graft [37]. However, portal venous drainage is likely to increase in popularity, given some reports that rejection rates are lower in this category [124,129]. Recent modifications include a retroperitoneal portal-enteric drainage technique behind the right colon [130].
3. Choice of graft, whole-organ or segmental: Almost all deceased donor pancreas transplants performed today are whole-organ grafts. Segmental grafts have little role to play in this group, except when a rare anatomic abnormality is noted such that the head of the pancreas cannot be used. A rare instance of a split deceased donor pancreas organ transplanted into two different recipients has been described [131]. All living donor pancreas transplants use segmental grafts (body and tail), which are still capable of maintaining normoglycemia in the recipient.

POSTOPERATIVE CARE

After an uncomplicated pancreas transplant, the recipient is transferred to the postanesthesia care unit or the surgical intensive care unit. Centers that have a specialized monitored transplant unit (with central venous and arterial monitoring capabilities) transition the postoperative recipients through the postanesthesia care unit to the transplant unit. Other centers transfer patients directly to the surgical intensive care unit for the first 24 to 48 hours. Care during the first few hours post transplant is similar to care after any major operative procedure. Careful monitoring of vital signs, central venous pressure, oxygen saturation, urine output, and laboratory parameters is crucial. The following factors are unique to pancreas recipients and should be attended to:

1. Blood glucose levels: Any sudden, unexplained increase in blood glucose levels should raise the suspicion of graft thrombosis. An urgent ultrasound must be done to assess blood flow to the graft. Some centers believe that maintenance of tight glucose control (less than 150 mg per dL) using an IV insulin drip is important to "rest" the pancreas in the early postoperative period.

2. Intravascular volume: Because the pancreas is a "low-flow" organ, intravascular volume must be maintained to provide adequate perfusion to the graft. Central venous pressure monitoring is used to monitor intravascular volume status. In some cases, such as patients with depressed cardiac function, pulmonary artery catheter monitoring may be required during the first 24 to 48 hours. If the hypovolemia is associated with low hemoglobin levels, then packed red cell transfusions should be given; otherwise, crystalloid (and sometimes colloid) replacement should be used to treat hypovolemia.
3. Maintenance IV fluid therapy: The choice of IV fluid therapy can be 5% dextrose in 0.45% normal saline, as long as IV insulin is used to maintain tight blood glucose control, or 0.45% normal saline to maintain acceptable urine output. In SPK recipients, whose IV fluid rate is based on urine output, dextrose should be eliminated if the urine output is high (more than 500 mL per hour), because hyperglycemia may cause an osmotic diuresis leading to worsening hypovolemia. Maintenance IV fluid for BD recipients should also include HCO_3 10 mEq per L to account for the excess HCO_3 loss, or sodium lactate can be used as an alternative.
4. Antibiotic therapy: Broad-spectrum antibiotic therapy (with strong Gram-positive and Gram-negative coverage) and antifungal therapy are instituted in the perioperative period. Antiviral prophylaxis is similar to that for other solid organs and is driven by cytomegalovirus (CMV) status.
5. Anticoagulation: At the University of Texas Health Science Center at San Antonio all pancreas recipients receive enteric-coated aspirin 81 mg started on first postoperative day and continued indefinitely. Recipients of solitary pancreas transplants or "high-risk" SPK transplants also receive an intraoperative dose of heparin (2,500 units), followed by a postoperative regimen of low-dose, continuous IV heparin at 300 units per hour for 24 hours, then 400 units per hour for 24 hours, then 500 units per hour for 5 postoperative days, at which time the IV heparin is discontinued and warfarin begins for 6 months. The partial thromboplastin time for heparin and the international normalized ratio for warfarin are not measured because these drugs are "low dose". Our experience is that therapeutic doses of heparin lead to excessive postoperative hemorrhage that requires reduction in heparin dose, and sometimes red cell transfusion or reoperation.

Immunosuppression

Immunosuppression is essential to thwart rejection in all allotransplant recipients. Before the advent of cyclosporine in the early 1980s, dual therapy with azathioprine and prednisone was the mainstay of immunosuppression for pancreas transplants. From the early 1980s to the mid-1990s, cyclosporine was introduced for maintenance therapy and resulted in significant improvement in immunologic outcomes. Since the mid-1990s, tacrolimus and mycophenolate mofetil have replaced cyclosporine and azathioprine as the primary maintenance immunosuppressive medications. In a prospective, randomized, multicenter study of tacrolimus versus cyclosporine in SPK recipients, Saudek et al. noted that 3-year patient and kidney graft survival were comparable but pancreas graft survival was superior in the tacrolimus-treated cohort (89% tacrolimus vs. 74% cyclosporine) [132]. In addition, with antibody induction steroids have been successfully withdrawn or even avoided in some cases [133,134]. The use of rapamycin in combination with tacrolimus has also allowed for steroid withdrawal or avoidance in some pancreas recipients [135,136]. Specific immunosuppressive regimens vary among different transplant programs. The immunosuppressive protocols for pancreas transplantation for the University of Texas Health Science Center at San Antonio in Table 184.3.

Antibody induction has become mainstay protocol for pancreas recipients. The debate continues as to which antibody preparations are best in pancreas transplant recipients [137]. The administration of depleting agents such as rabbit antithymocyte globulin (rATG) or alemtuzumab has increased dramatically in the last few years, while the use of IL-2 inhibitors has decreased, with the rationale that depleting antibodies provide good immunosuppressive coverage for innovative immunosuppressive strategies including steroid withdrawal or avoidance, minimization of calcineurin inhibitors and even monotherapy in pancreas transplant patients [138]. When combined with steroid withdrawal, minimization of calcineurin inhibitors may require prolonged antibody therapy, which may increase the risk of infection [138].

Results

Outcomes after pancreas transplants have consistently improved over the years. The 2008 SRTR report [48] described pancreas transplant graft and patient survival over the decade from 1997 to 2008. Unadjusted graft survival rates for SPK, PAK, and PTA recipients were 84%, 78%, and 75%, respectively, for year 2006, whereas patient survival rates were similar in all 3 groups (SPK 95%, PAK 97%, PTA 98%) [62]. Those recipients who received SPK transplants experienced the best unadjusted long-term graft survival rates: 73% at 5 years and 53% at 10 years. Graft survival rates for PAK and PTA recipients were statistically lower than SPK recipients, with 5-year rates of 54% and 51%, respectively, and 10-year rates of 35% and 26%, respectively.

The latest report from the IPTR [40] focused on United States pancreas transplants from 2000 to 2004, and included more than 3,800 SPK, more than 600 PAK, and 290 PTA cases. One-year patient survival rates for all three categories were more than 95%. One-year pancreas graft survival rates were higher for SPK (85%) than for PAK (78%) and PTA (76%) recipients. Graft loss from rejection at 1 year was low in all three categories (2% SPK, 8% PAK, 10% PTA). In the majority of all transplants, ED was used for duct management, and of the ED transplants, portal venous drainage was used in 25% of cases. Although overall graft function did not vary with ED or BD, the PTA group had a higher immunologic graft loss rate in ED versus BD cases. BD may result in earlier diagnosis of rejection because of the ability to monitor decreased urinary amylase levels as a marker. Nevertheless, the late rejection rate was higher in the PTA than in other categories.

Donor and Recipient Causes of Pancreas Complications

Donor and recipient factors can influence the postoperative course after pancreas transplantation. In a study of 210 SPK transplants between 1995 and 2007, donor-specific risk factors correlating with postoperative pancreas-related complications included donor age, need for vasopressor support, need for preprocurement blood transfusions, and asystolic events > 10 minutes [139]. Increasing donor age and BMI were associated with greater need for postoperative interventions. Graft preservation with HTK solution was associated with significantly higher postoperative complications, as was preexisting cardiac disease in the recipient. The choice of immunosuppression had a significant effect on pancreas-related complications,

TABLE 184.3

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO STANDARD IMMUNOSUPPRESSION-PANCREAS PROGRAM

SPK[a]	PAK[b] and PTA[c]	Rejection
Antithymocyte globulin 1.5 mg/kg: Three doses QOD First dose intraoperatively Give methylprednisolone 250 mg before first dose 100 mg before second dose Give premeds before all doses— diphenhydramine and acetaminophen Monitor ALC[d], platelet count	**Antithymocyte globulin** 1.5 mg/kg: Three doses QOD First dose intraoperatively Give methylprednisolone 250 mg before first dose 100 mg before second dose Give premeds before all doses— diphenhydramine and acetaminophen Monitor ALC, platelet count	Methylprednisolone Day 0–4: 1,000 mg IV[h] Resistant rejection Antithymocyte globulin 1.5 mg/kg IV up to 7 days Give methylprednisolone 250 mg IV before first dose 100 mg before second dose Give premeds before all doses— diphenhydramine and acetaminophen Monitor ALC, platelet count
Tacrolimus 5 mg po[e] b.i.d.[f] Start when creatinine < 4 mg/dL If tacrolimus is delayed continue ATG[g] until tacrolimus levels are therapeutic Levels 8–10 ng/mL for 3 mo Then 5–8 ng/mL	Tacrolimus 5 mg po b.i.d. Start postoperatively If tacrolimus is delayed continue ATG until tacrolimus levels are therapeutic Levels 8–10 ng/mL for 3 mo Then 5–8 ng/mL	
Mycophenolate 500 mg po b.i.d. until ATG is removed, then 1 g po b.i.d.	Mycophenolate 500 mg po b.i.d. until ATG is removed, then 1 g po b.i.d.	

Round up antithymocyte globulin dose to the nearest 25 mg.
ALC Levels: if zero, hold antithymocyte globulin; if 0.1, give half dose antithymocyte globulin; if 0.2 or above, give full dose.
ATG requires "premeds" with methylprednisolone for first three doses, and diphenhydramine and acetaminophen for all doses.
[a]SPK, simultaneous pancreas kidney.
[b]PAK, pancreas after kidney.
[c]PTA, pancreas transplant alone.
[d]ALC, absolute lymphocyte count.
[e]po, orally.
[f]b.i.d., twice daily.
[g]ATG, antithymocyte globulin.
[h]IV, intravenously.

which were greater after induction therapy with rATG versus daclizumab, and maintenance immunosuppression with tacrolimus/rapamycin or cyclosporine/mycophenolate mofetil versus tacrolimus/mycophenolate mofetil. The duration of the pancreas transplant operation and the presence of elevated C reactive protein were associated with significantly more postoperative complications that required interventions. In another study, donor obesity (BMI > 30 kg per m^2) was associated with greater risk of graft thrombosis and deep wound infections [140]. Another trial [141] noted that technical failure of the pancreas graft occurred more commonly when (1) the donor BMI was > 30 kg per m^2, (2) the cause of donor death was other than trauma, (3) the preservation time was > 24 hours, (4). the duct management was ED versus BD, and (5) recipient BMI was > 30 kg per m^2. In other study [142], multivariate analysis showed that technical failure of a pancreas transplant appeared to be the most significant risk factor for kidney graft loss. This evidence underscores that careful donor and recipient selection in addition to improved preservation and surgical techniques play important roles to minimize complications after pancreas transplantation [143].

Surgical Complications

Prevention of surgical complications has critical implications not only on pancreas graft and patient survival, but also on financial impact associated with postoperative care. Early diagnosis and management of surgical complications can limit morbidity; delayed diagnosis, and treatment of pancreas complications can lead not only to pancreas graft loss but also kidney graft loss [143,144]. Common surgical complications in pancreas transplants will now be addressed:

1. Hemorrhage: Postoperative hemorrhage is a frequent reason for early re-laparotomy in pancreas transplant recipients. Hemorrhage can occur from the pancreatic parenchyma, from poorly ligated mesenteric or splenic vascular stumps or from the anastomosis in an enteric-drained or bladder-drained pancreas transplant. The incidence of hemorrhage ranges from 6% to 7% [85], and this risk increases with the use of anticoagulation in the immediate postoperative period. Frequent physical examination and monitoring of hemoglobin help to detect early hemorrhage. Heparin may be temporarily suspended to stabilize the patient. Packed cells should be administered if the recipient has symptomatic anemia. If hemorrhage continues, early operative intervention is indicated. If hemorrhage slows down or ceases, heparin should be resumed at a lower rate and judiciously increased as tolerated.
2. Thrombosis: Thrombosis post transplant ranges from 5% to 6% [85], and remains the most common cause of early pancreas graft failure. The risk increases after segmental

pancreas transplantation because of the small caliber of vessels [145]. Most pancreas transplant thromboses are due to technical causes. Diagnosis is suspected by sudden hyperglycemia and confirmed by sonogram, CT angiogram, formal angiogram, or MRI, which reveals pancreas graft thrombosis. Aggressive anticoagulation will not prevent pancreas transplant thrombosis due to technical reasons. A short portal vein requiring an extension graft or atherosclerotic arteries in the pancreas graft increases the risk for thrombosis. In the recipient, a narrow pelvic inlet with a deeply placed, poorly immobilized iliac vein, atherosclerotic disease of the iliac artery, a technically difficult vascular anastomosis, kinking of the vein by the pancreas graft, significant hematoma formation around the vascular anastomosis, hypovolemia, and a hypercoagulable state are some of the factors that increase the risk for thrombosis. The most common form of hypercoagulable state in the Western population is factor V Leiden mutation. Its incidence ranges from 2% to 5% but may be as high as 50% to 60% in patients with a history (self or family) of vascular thrombosis [146]. Other causes of hypercoagulable state include antithrombin III deficiency, protein C or S deficiency, activated protein C resistance and anticardiolipin antibodies [147]. The transplant surgeon must have a high incidence of suspicion of these hypercoagulable states and treat them aggressively to prevent pancreas graft thrombosis. Thrombosis is diagnosed by sudden hyperglycemia and by imaging studies that show nonpatent pancreatic vessels. Thrombosis usually necessitates transplant pancreatectomy.

3. Duodenal stump leaks: The incidence of duodenal stump leaks ranges from 6% to 7% [85]. A leak from the anastomosis of the duodenum stump to the bowel almost always leads to re-laparotomy. Gross peritoneal contamination due to an enteric leak usually necessitates a graft pancreatectomy. The diagnosis is made by elevated pancreatic enzymes in a patient who has clinical signs of acute abdomen. A plain abdominal radiograph may show free air, and an abdominal CT scan may show free air and extravasation of contrast into the free peritoneal cavity. The differential diagnosis is pancreatitis, abdominal infection, or acute severe rejection. A roux-en-Y anastomosis to the duodenal stump may be a preferred technique, if the risk of leak is thought to be increased during the initial pancreas operation. Other novel techniques such as a venting roux-en-Y-pancreatic duodenojejunostomy have been used in selected recipients [148].

   Small duodenal stump leaks in bladder-drained recipients are usually managed nonoperatively with prolonged catheter decompression of the urinary bladder. The diagnosis of duodenal stump leak is made using plain or CT cystography. Large leaks may require operative intervention, including primary repair, enteric conversion, or even transplant pancreatectomy if there is significant compromise of the duodenal stump.
4. Major intra-abdominal infections: The incidence of significant intra-abdominal infections requiring reoperation ranges from 3% to 4% [85]. Performance of the enteric anastomosis with associated contamination predisposes to this higher rate of intra-abdominal infection, where fungal and Gram-negative organisms predominate. With the advent of percutaneous procedures to drain intra-abdominal abscesses, the incidence of reoperations is fast decreasing. If the infection is uncontrolled or widespread, then graft pancreatectomy followed by frequent washouts may be necessary.
5. Renal pedicle torsion: Torsion of the kidney has been reported after SPK transplants [149,150]. The intraperitoneal location of the kidney (allowing for more mobility) predisposes to this complication. Additional risk factors are a long renal pedicle and a marked discrepancy between the length of artery and vein. Prophylactic nephropexy to the anterior or lateral abdominal wall is recommended with intraperitoneal transplants to avoid this problem. The colon can be mobilized and re-approximated over a kidney transplant in order to prevent torsion also.
6. Others: Other surgical complications that may require re-laparotomy include wound dehiscence, incisional hernia, severe pancreatitis (sometimes hemorrhagic or necrotic), pseudocysts, pseudoaneurysms, arteriovenous (AV) fistula in the graft, severe painful rejection and bowel obstruction [151]. The overall incidence of re-laparotomy for these complications decreased from 32% in the 1980s to 19% in the 1990s, and the mortality rate in recipients requiring re-laparotomy decreased from 9% to 1% over that same period. Improved antibiotic prophylaxis, surgical techniques, immunosuppression, and advances in interventional radiology have all contributed to this decrease [85].

Nonsurgical Complications

1. Pancreatitis: The incidence of posttransplant pancreatitis varies based on the type of exocrine drainage. Bladder-drained recipients with abnormal bladder function are at increased risk of pancreatitis secondary to incomplete bladder emptying and urinary retention causing resistance to flow of pancreatic exocrine secretions. Other causes of pancreatitis include drugs (corticosteroids, azathioprine, cyclosporine), hypercalcemia, viral infections (CMV or hepatitis C), and reperfusion injury after prolonged ischemia. Pancreatitis is usually manifested by an increase in serum amylase and lipase with or without local signs of inflammation. An abdominal ultrasound or CT scan may identify an enlarged, edematous, hypoechoic pancreas transplant. The treatment usually consists of catheter decompression of the bladder for a period of 2 to 6 weeks, depending on the severity of pancreatitis. In addition, octreotide therapy may be used to decrease pancreatic secretions. The underlying urologic problem, if any, should be treated. The patient should be placed on NPO status and total parenteral nutrition should be administered if the pancreatitis is severe. If repeated episodes of pancreatitis occur, enteric conversion of a bladder-drained pancreas transplant may be indicated.
2. Rejection: The incidence of acute rejection ranges from 15% to 30% and immunologic graft loss from 2% to 15% for all types of pancreas transplants at 1 year [3]. The diagnosis is usually based on increased serum amylase and lipase levels in all pancreas transplant patients, and decreased urinary amylase levels in bladder-drained recipients. A sustained drop in urinary amylase levels from baseline should prompt a pancreas biopsy to rule out rejection. In enteric-drained recipients, one has to rely on serum amylase and lipase levels only. A rise in serum lipase levels has shown to correlate well with acute rejection in the pancreas transplant. Other signs and symptoms include tenderness over the graft, unexplained fever, and hyperglycemia (which is usually a late finding). Diagnosis of rejection can be suspected by a hypoechoic, enlarged graft by ultrasound or an enlarged, edematous graft by abdominal CT scan. Diagnosis of rejection can be confirmed by a percutaneous pancreas biopsy [152]. In cases in which percutaneous biopsy is not possible due to technical reasons, empiric therapy for rejection may be started. Rarely, open biopsy is indicated, and transcystoscopic biopsy of a bladder-drained pancreas graft, which was used in the past, has been largely abandoned. Finally, in SPK recipients, isolated pancreas transplant rejection portends a worse renal allograft survival than in patients who experience no rejection [153].

3. Others: Other findings include infectious complications such as CMV, extra-abdominal bacterial or fungal infections, posttransplant malignancy such as posttransplant lymphoproliferative disorder, and other rare complications such as graft-versus-host disease. Many catheter infections are due to Gram-positive organisms, with methicillin resistant coagulase negative isolates quite common [154]. The diagnosis and management of these complications is similar to those of other solid-organ transplants.

Radiologic Studies

1. Ultrasonography: This is the most frequent study used in pancreas recipients. Noninvasive, portable, and relatively inexpensive, it provides prompt information regarding blood flow to the pancreas, the presence of arterial or venous stenosis or occlusion, thrombosis, pseudoaneurysms, AV fistulae, resistance to blood flow within the pancreas (suggestive of either rejection or pancreatitis) and peripancreatic fluid collections.
2. CT scan: A CT scan provides more detail of pancreatic and surrounding anatomy. Use of oral, IV, and bladder contrast (in bladder-drained recipients) is recommended. Thus, a CT cystogram can be combined with an abdominal CT scan. A CT scan is frequently used as a guide in pancreas biopsies or in placement of percutaneous drains for intra-abdominal infection.
3. Fluoroscopy: A contrast cystogram can be performed under fluoroscopy and can be used instead of, or in addition to, a CT cystogram to look for a bladder leak. The combination of the tests increases the sensitivity for detecting bladder leaks.
4. Magnetic resonance angiogram (MRA): An MRA is done if vascular abnormalities are suspected on the ultrasound. MRA provides accurate information about pancreatic vascular patency, but it is inferior to standard angiography in providing fine vascular detail.
5. Angiography: This is the gold standard test for evaluating arterial anatomy in and around the pancreas. However, it is rarely employed, except in cases in which angiographic intervention (such as angioplasty, stenting of a stenotic segment, or coiling of an AV fistula or pseudoaneurysm) is planned. Contrast nephropathy is feared in a solitary pancreas recipient with renal dysfunction, and reasonable alternatives (such as ultrasound) are available.

FUTURE DIRECTIONS

In type 1 diabetic patients with kidney dysfunction, an SPK or PAK transplant is the standard of care. A PTA, however, is less common because the long-term risks of diabetes are weighed against the long-term risks of immunosuppression. A successful pancreas transplant can improve existing neuropathy and nephropathy in diabetic recipients and the survival after a solitary pancreas transplant is better than remaining on the waiting list [155]. As the risks of immunosuppression decrease with novel methods of tolerance and immunomodulation, the balance will tilt in favor of an early transplant. The limiting factor will then be the organ shortage, which could be alleviated if xenotransplantation is able to overcome its current barrier of hyperacute rejection.

The application of islet transplants is rapidly growing. Recent successes suggest that islet transplants can provide all the benefits of pancreas transplants without the risks of major operation. Improvements in islet isolation, islet viability, islet functionality, islet implantation, and immunotherapy will improve islet outcomes, so that only one donor will be necessary to achieve insulin independence [156]. Xenotransplantation of islets may be more readily achievable using encapsulation than with other organs. Prolonged diabetes reversal after intraportal xenotransplant in primates has been documented [157] and may pave the way for human xenotransplant trials. Also, stem cells from numerous sources (e.g., bone marrow, adipose, or cord blood) may be manipulated to differentiate into islets in order to provide a rich supply for transplantation, and islet transplants can be combined with immunomodulation and tolerogenic strategies to minimize or eliminate immunosuppression [156]. This combination would provide for minimally invasive islet cell transplants for all type 1 diabetic patients without the need for long-term immunosuppression. The only scenario that would be better would be the thwarting of autoimmunity before the onset of isletitis, thereby preventing type 1 diabetes mellitus in the first place.

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CHAPTER 185 ■ MANAGEMENT OF THE ORGAN DONOR

CHRISTOPH TROPPMANN

In 2009, nearly 10,000 patients on the national organ transplant waiting list in the United States died or were de-listed because they had become too ill before a suitable donor organ became available [1]. Almost assuredly, this number underestimates the actual magnitude of the problem. Many patients with end-stage organ failure are currently not even considered for transplantation (and consequently are not listed) because of the strict recipient selection criteria that are being applied—in part as a result of the severe, ongoing organ shortage. The widening gap between available deceased donor organs and the number of patients waiting is a result of the explosive, increased use of organ transplantation therapy over the past 30 years (Tables 185.1 and 185.2), with which the deceased donor pool has not kept pace [1,2] (Fig. 185.1).

The single most important factor that has been identified in this equation is the failure to maximize the conversion of potential deceased donors to actual donors, primarily because of the inability to obtain consent for organ retrieval. The rates of consent granted by families of potential deceased donors range from 0% to 75% and appear to vary widely among geographic regions and ethnic groups [10–12]. The national average is only 54% [12]. Lack of dissemination and poor presentation of information to the public, misperceptions in the general population regarding the beneficial nature of organ transplantation and the necessity of organ retrieval from deceased donors, and inappropriate coordination of the approach to families of potential donors contribute to the stagnation of the organ supply [11–13].

The role of physicians who care for critically ill patients in altering the current situation is crucial. It is their responsibility to seek early referral to an organ procurement organization (OPO) and to ensure that families are adequately approached, thus laying the foundation for obtaining consent (Table 185.3). In the United States alone, approximately 250,000 additional life years could be saved annually if consent for potential deceased donors could be increased to 100% [14]. Intensive care and emergency medicine physicians are obligated ethically and morally to provide the best possible outcome for a very ill

TABLE 185.1

NUMBER OF SOLID ORGAN TRANSPLANTS FROM DECEASED DONORS PER YEAR IN THE UNITED STATES: 1982 VERSUS 2009

Organ	1982	2009
Kidney	3,681	11,296
Liver	62	6,101
Pancreas	38	1,233
Heart	103	2,211
Heart–lung	8	30
Lung	—[a]	1,659
Intestine	—[a]	178

[a]No lung or intestinal transplants were performed in 1982.
Data from references [1–4].

TABLE 185.2

ONE-YEAR GRAFT SURVIVAL RATES (DECEASED DONORS): 1982 VERSUS 2008

Organ	1982[a] (%)	2008 (%)
Kidney	80	91
Liver	35	82
Pancreas	23	86
Heart	65	87
Lung	—[b]	82
Intestine	—[b]	68

[a]Results without cyclosporin A–based immunosuppression.
[b]No lung or intestinal transplants were performed in 1982.
Data from references [4–8] (1982) and [1,2] (2008).

TABLE 185.3

IDENTIFICATION OF POTENTIAL ORGAN DONORS: GUIDELINES FOR REFERRAL TO THE LOCAL ORGAN PROCUREMENT ORGANIZATION

Clinical triggers	All severely neurologically injured patients on a ventilator with any of the following conditions: Head trauma Cerebral hemorrhage Primary brain tumor Hypoxic insult (including prolonged CPR, near drowning, drug overdose, poisoning, cerebral edema, seizures, and asphyxiation injuries)
Referral guidelines	Refer all patients who meet clinical triggers regardless of age and underlying/associated diagnosis Refer all patients who meet clinical triggers *prior* to approaching the family regarding end-of-life decisions Refer patients prior to brain death evaluation Refer patients if the family raises the subject of donation Coroner case status does *not* constitute an exclusion criterion

patient. However, after a potential donor has been identified, they are also obligated to seek the best possible outcome for patients with end-stage failure of a vital organ waiting for a transplant by attempting to ensure that organ donation occurs. It is becoming increasingly evident that implementation of critical pathways and standardized donor management protocols play an important role in this context [15–25).

DONOR CLASSIFICATION

Brain-Dead Deceased Donors

This is by far the most common donor type (currently 90% of all donors belong in this category) [2]. In most Western developed countries, brain death is legally equated with death. The diagnosis of brain death rests on the irreversibility of the neurologic insult and the absence of clinical evidence of cerebral *and* brainstem function. The details of the clinical examination that is required to unequivocally establish brain death are described later in this chapter. Organ procurement proceeds only after brain death has been diagnosed and death has been declared.

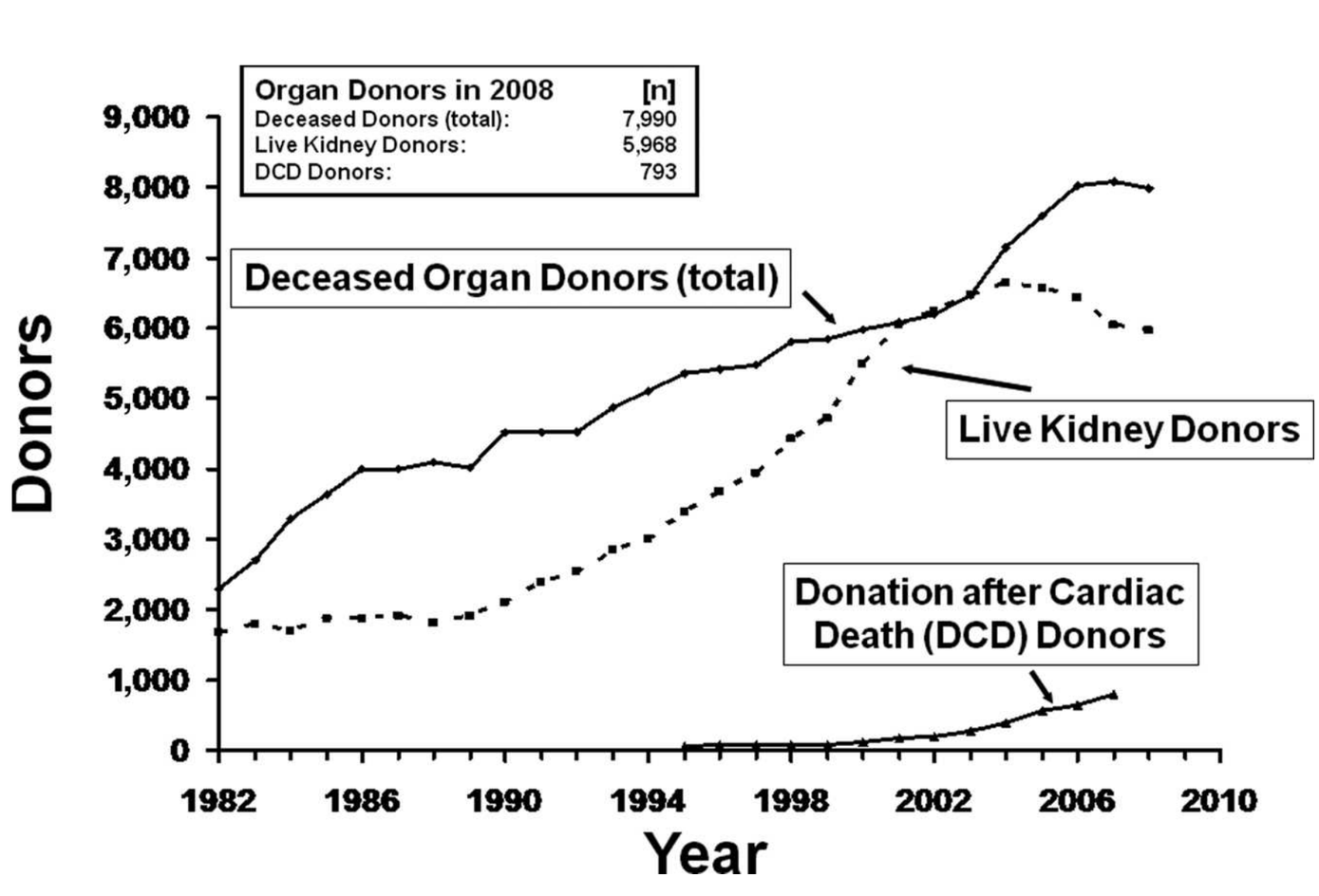

FIGURE 185.1. Evolution of the number of deceased organ donors and living kidney donors between 1982 and 2008 in the United States. (Data from references [1–4,9].)

Donation after Cardiac Death Donors (Formerly Known as Non–Heart-Beating Donors)

Increases in this donor category are to be expected over coming years (Fig. 185.1) [1,2,24,26,27]. Most frequently, families of unconscious patients with severe irreversible traumatic or cerebrovascular brain injury, who do not fulfill the formal criteria of brain death, decide to forgo any further life support treatment and wish to donate the organs of their family member. Time and place of death are therefore controlled. The prospective donor is brought to the operating room and life support treatment is discontinued. Organ procurement is initiated once death has been pronounced by a physician not belonging to the organ recovery and transplant team [26].

An alternative, by far less common scenario—uncontrolled death—involves a patient who expires, for example, in the emergency room following massive trauma or a sudden cardiovascular event. In the interest of minimizing warm ischemia time, flushing cannulas would then have to be inserted and possibly even perfusion of internal organs with cold preservation solution would already have to be started while consent to proceed with organ donation is obtained from the patient's family. Issues that specifically surround this category of donation after cardiac death (DCD) donors have generated considerable debate within the medical community. These issues include ethical concerns centered on when to stop the resuscitation effort and whether it is ethical to perform a procedure (i.e., insertion of flushing cannulas) that presumes consent before actually obtaining it from the family. Other considerations that pertain to both controlled and uncontrolled death DCD donors and that have undergone intense debate, too, include establishing a definition of death after discontinuing life support (there is no commonly accepted definition of, for example, the minimal duration of asystole after the patient expires following withdrawal of support before death can be pronounced; this is currently subject to considerable interinstitutional variation), the possibility of the patient at least temporarily surviving the withdrawal of support systems (backup plans must be clearly defined by each individual institutional DCD donor protocol), and the conflict between providing optimal care for the patient and promoting suitable organ procurement and maintaining donor organ viability [28,29]. Nevertheless, these concerns must be contrasted with the right of self-determination and the final wishes of a competent patient family. Further debate by the medical community and general public is crucial to resolving these complex moral and ethical issues [28,29]. Without such thorough consideration, the deceased donor concept and the donation system that is currently in place might be harmed or discredited.

CURRENT STATUS OF SOLID-ORGAN TRANSPLANTATION

The increased number of solid-organ transplant procedures performed during the last 30 years has been paralleled by a significant improvement in outcome with regard to patient and to allograft survival (Table 185.2). This phenomenon has been attributed to a variety of factors that include (a) the introduction in the early 1980s of the powerful immunosuppressive agent cyclosporin A, followed almost a decade later by tacrolimus, mycophenolate mofetil, and other new immunosuppressants; (b) the availability of antilymphocyte antibody preparations to prevent and treat rejection episodes (e.g., antilymphocyte and antithymocyte globulin); (c) improvements in organ preservation (e.g., use of University of Wisconsin solution); (d) thorough preoperative patient screening for the presence of existing disease processes; and (e) increasing sophistication in the postoperative intensive care of regular as well as high-risk recipients. In addition, the availability of potent, yet nontoxic, antibacterial, antifungal, and antiviral agents has allowed opportunistic infections in immunocompromised transplant patients to be treated more effectively. In combination with refinement of surgical techniques, these factors have led to increasing success of solid-organ replacement therapy.

Thus, transplantation has become the treatment of choice for many patients with end-stage failure of the kidneys, liver, endocrine pancreas, heart, lungs, and small bowel. Successful hand, arm, larynx, and face transplants from deceased donors have also been reported [30–33]. Criteria for potential recipients have been expanded over the past five decades to include infants, children, and individuals previously thought to be at higher risk for complications (e.g., diabetics, elderly patients). Currently, the only patients who are excluded from undergoing transplantation are those with malignancies (metastatic or at high risk for recurrence), uncontrolled infections, those who are unable to withstand major surgery, or those who have a significantly shortened life expectancy due to disease processes unrelated to their organ dysfunction or failure.

Kidney

Currently, patients undergoing kidney transplants from deceased donors exhibit excellent graft survival rates (91% and 68% at 1 and 5 years, respectively) [1,2]. Renal transplantation dramatically improves life expectancy and quality of life, decreases cardiovascular morbidity, and rehabilitates the recipients from a social perspective. Kidney transplants are also less expensive from a socioeconomic standpoint than is chronic hemodialysis. For pediatric patients with chronic renal failure, a functioning renal allograft is the only way to preserve normal growth and ensure adequate central nervous, mental, and motor development.

Liver

Patients with end-stage liver failure die unless they receive a transplant. Liver transplants are an effective treatment for many patients, pediatric and adult, regardless of the cause of liver failure: congenital (i.e., structural or metabolic defects), acquired (i.e., due to infection, trauma, or intoxication), or idiopathic (e.g., cryptogenic cirrhosis, autoimmune hepatitis). A dramatic improvement in graft survival occurred after the introduction of cyclosporin A (Table 185.2). Currently, there are no reliable means to substitute, even temporarily, for a failing liver other than with a transplant. Extracorporeal perfusion, using either animal livers or bioartificial liver devices (e.g., hepatocytes suspended in bioreactors), may someday bridge the gap between complete liver failure and a liver transplant, but these therapeutic modalities are still investigational and are far from becoming standard clinical tools. Use of hepatocyte and stem cell transplants to treat fulminant liver failure and to correct congenital enzyme deficiencies is also in the preliminary stages of study.

Small Bowel

Small bowel transplants are being performed increasingly in patients with congenital or acquired short gut, especially if liver dysfunction occurs because of long-term administration of total parenteral nutrition and if difficulty in establishing or

maintaining central venous access occurs. If liver disease is advanced, a combined liver–small bowel or, in highly selected cases, a multivisceral transplant (liver, stomach, small bowel, with or without pancreas) can be performed. Current results are encouraging, and a further increase in the number of small bowel and multivisceral transplants can be expected over the next decade [1,2,34].

Pancreas and Islet

Primary prevention of type 1 insulin-dependent diabetes mellitus is not possible at present, but transplantation of the entire pancreas or isolated pancreatic islets can correct the endocrine insufficiency once it occurs. Glucose sensor systems that *continuously* monitor blood sugar levels coupled with real-time command of an insulin delivery system (implantable pump) are not yet available for routine clinical use. Development of bioartificial and hybrid biomechanical insulin-secreting devices is in the experimental stages. The only effective current option to *consistently* restore continuous near-physiologic normoglycemia, however, is a pancreas transplant [35–37]. Good metabolic glycemic control decreases the incidence and severity of secondary diabetic complications (neuropathy, retinopathy, gastropathy and enteropathy, and nephropathy). Most pancreas transplants are performed simultaneously with a kidney transplant in preuremic patients with significant renal dysfunction or in uremic patients with end-stage diabetic nephropathy. Selected nonuremic patients with brittle type 1 diabetes mellitus (with progression of the autonomic neuropathy to the point of hypoglycemic unawareness, and with repetitive episodes of diabetic ketoacidosis) can benefit from a solitary pancreas transplant (without a concomitant kidney transplant) to improve their quality of life and to prevent the manifestation and progression of secondary diabetic complications. Evidence suggests that a successful pancreas transplant can achieve these goals in uremic and in nonuremic recipients and decrease mortality [35]. Islet transplants are undergoing intensive clinical investigation. Results of transplanting alloislets from deceased donors are encouraging in the short term [36]; however, long-term results have been relatively disappointing [37]. Nonetheless, with further progress to be expected, islet transplants may become a routine form of therapy for patients with complicated diabetes within the next 10 years.

Heart

Heart transplants are the treatment of choice for patients with end-stage congenital and acquired parenchymal and vascular diseases and are recommended generally after all conventional medical or surgical options have been exhausted. After a widely publicized start in 1967, poor results were observed over the ensuing decade. In the 1980s, however, the field of cardiac transplantation experienced dramatic growth (Table 185.1) because of significant improvements in outcome, probably most directly related to immunosuppressive therapy and to refinements in diagnosis and treatment of rejection episodes [38]. Mechanical pumps, such as ventricular assist devices or the bioartificial heart, serve only to bridge the time between end-stage cardiac failure and a transplant and are by no means a permanent substitute for the transplant itself.

Heart–Lung and Lung

Heart–lung and lung transplants are effective treatment for patients with advanced pulmonary parenchymal or vascular disease, with or without primary or secondary cardiac involvement. This field has evolved rapidly since the first single-lung transplant with long-term success was performed in 1983 (Table 185.1). The significant increase in lung transplants is mainly due to technical improvements resulting in fewer surgical complications, as well as to the extremely limited availability of heart–lung donors. Previously, many patients with end-stage pulmonary failure would have waited for an appropriate heart–lung donor. Currently, they undergo a single or a bilateral single-lung transplant instead [39]. Bilateral single-lung transplants are specifically indicated in patients with septic lung diseases (e.g., cystic fibrosis, α_1-antitrypsin deficiency) in which the remaining native contralateral lung could cross-contaminate a single transplanted lung. Double en bloc lung transplants have been abandoned because of technical difficulties related to the bronchial anastomotic blood supply. Mechanical ventilation or extracorporeal membrane oxygenation can be used as a temporary bridge to this type of transplant, but use of these modalities does not obviate the need for organ replacement therapy.

CURRENT STATUS OF ORGAN DONATION

The once steady increases in most types of organ transplant procedures have considerably slowed or reached a plateau over the last several years. This is due to an insufficient augmentation of the donor pool (Tables 185.1 and 185.2; Fig. 185.1). The 55-mile-per-hour speed limit, stricter seat belt and helmet laws, and improved trauma care have all had a significant impact on the number of available brain-dead organ donors [1]. As a consequence, substantial nationwide changes in cause-of-death patterns for brain-dead donors were observed between 1988 and 2008. Head trauma deaths decreased from 34% to 16% of total deaths, whereas cerebrovascular deaths increased from 29% to 41% [1,2]. In 2008, the three leading causes of death among brain-dead donors in the United States were cerebrovascular accidents, blunt head injuries, other cardiovascular events (e.g., myocardial infarctions), followed by gunshot or stab wounds, and other miscellaneous causes [1,2].

To improve organ availability in the face of the donor crisis, the United States Department of Health and Human Services (DHHS) launched at the beginning of the new millennium several national Organ Donation and Organ Transplantation Breakthrough Collaborative initiatives [24,26,40,41]. These were designed to develop and share best practices among donor hospitals, organ procurement organizations, and transplant centers throughout the United States. The initiatives called on the participants to reach a 75% conversion rate (the number of actual donors divided by the number of potential donors) and a 3.75 organs-transplanted-per-donor average yield rate [24,26,40,41]. In large part due to these initiatives and other ongoing national efforts, an encouraging increase of the number of deceased donors in the United States has been observed over the past decade (Fig. 185.1) [1,2,24,26]. Most recently, however, the number of organ donors in the United States has begun to stagnate again (Fig. 185.1) [1,2].

A positive trend that has started to take place is the increasing number of DCD donors (Fig. 185.1) [2,24]. These donors constitute currently 10% of the overall deceased donor pool [2]. Further increases over the coming years are to be expected as the overall organ donor shortage will continue to worsen. In DCD donors, refined surgical techniques allow for fast insertion of cannulas and perfusion of vital organs while these are rapidly excised. Innovative approaches, such as withdrawal of care in the ICU (rather than in the operating room), in the presence of the donor's family, may further increase acceptance of DCD donation among potential donors' families

and health care personnel [26,29]. Moreover, refinements of organ perfusion and preservation techniques, including maintenance of the DCD donor on extracorporeal membrane oxygenation (ECMO) until organ recovery can occur, and placement of the recovered organs on pulsatile perfusion pumps during the transport and preservation phase, result in less ischemic organ injury, and allow for better organ preservation and increased use of DCD donor organs, too [24,42–44]. Currently, kidneys and livers are the organs most commonly recovered and transplanted from DCD donors [2].

According to estimates, there are at least 10,500 to 13,800 *potential* brain-dead donors in the United States per year [12]. In 2010, however, there were only 7,944 *actual* deceased organ donors in the United States [1]. In a recent study, the overall consent rate (the number of families agreeing to donate divided by the number of families asked to donate) was 54% in the United States, and the overall conversion rate was 42% [12]. The single most important reason for lack of organ retrieval from 45% to 60% of the potential donor pool is the inability to obtain consent [12,24]. Several studies have shown that family refusal to provide consent and the inability to identify, locate, or contact family members to obtain consent within an appropriate time frame are the leading causes for the nonuse of many potential donors [10–13,24]. A public opinion survey showed that 69% of respondents would be very or somewhat willing to donate their organs, and 93% would honor the expressed wishes of a family member [45]. However, only 52% of these individuals had communicated their wishes to their family. Moreover, 37% of respondents did not comprehend that a brain-dead person should be considered dead and unable to recover, and 59% either believed or were unsure whether or not organs can be bought and sold on the "black market." Also, 42% did not realize that organ donation does not cause any financial cost to the family of the deceased in the United States [45].

Correcting these misperceptions and attempting to increase awareness of the importance of organ transplant must remain the focus of public educational campaigns [24,29]. The family's knowledge of the patient's previous wishes is central to decision making [10,11,13]. Such efforts can be successful, especially among minorities, in whom mistrust and the perception of inequitable access to medical care and organ transplant therapy have led to disappointingly low organ donation and recovery rates [24,46]. It is very important that adequate communication, empathy, and an informative, humane approach to the family of the deceased occur to ensure reasonable consideration of donation. Families are more likely to donate if they are approached by an organ procurement organization coordinator, view the requestor as sensitive to their needs, and experience an optimal request pattern [11,13,21,22]. Educational efforts to enhance organ donation must therefore also be directed at health care professionals and medical students, whose views and knowledge of these issues are often inconsistent and limited [29,47]. Physicians, too, need to be better trained to recognize and refer potential organ donors and to not discuss organ donation until a member of the local organ procurement organization has approached their families [11,13,21,22].

OPTIONS TO INCREASE ORGAN AVAILABILITY

Mechanisms that might serve to increase the number of available organs for transplantation include (a) optimization and maximal use of the current actual donor pool; (b) increasing the number of living donor transplants, including the provision of incentives for live donation; (c) use of other unconventional and controversial donor sources, such as anencephalic donors and executed prisoners; and (d) xenotransplants (e.g., use of animal organs as a potentially unlimited supply for transplantation into humans, particularly after genetic engineering) [48]. The first two mechanisms are of current practical interest, whereas the last two are likely to continue to confront critical care and transplant physicians, nurses, and the lay population over the next years in the form of an ongoing, public debate.

Optimal Use of the Current Donor Pool

As a result of the ongoing organ shortage, transplant surgeons have attempted to refine procurement techniques so that maximal use of the available donor pool occurs [49] (Fig. 185.2). For example, currently more than 85% of all deceased donors are multiple-organ donors. On average, more than three organs are recovered and transplanted from each deceased donor [1,2,24,40,41] (Fig. 185.2). Extension of the organ preservation time by a variety of techniques, including new preservation solutions and pulsatile perfusion preservation, has facilitated allocation of organs to geographically distant transplant centers [44].

Marginal donors—elderly patients, patients with a history of hypertension, poisoning victims, patients with significant organ injury (e.g., liver laceration due to blunt injury), or complications of brain death (e.g., hypotension, oliguria or anuria, disseminated intravascular coagulation)—are now used almost routinely for recovery of kidneys and of extrarenal organs [1,2,24]. Procurement techniques also have been adapted to

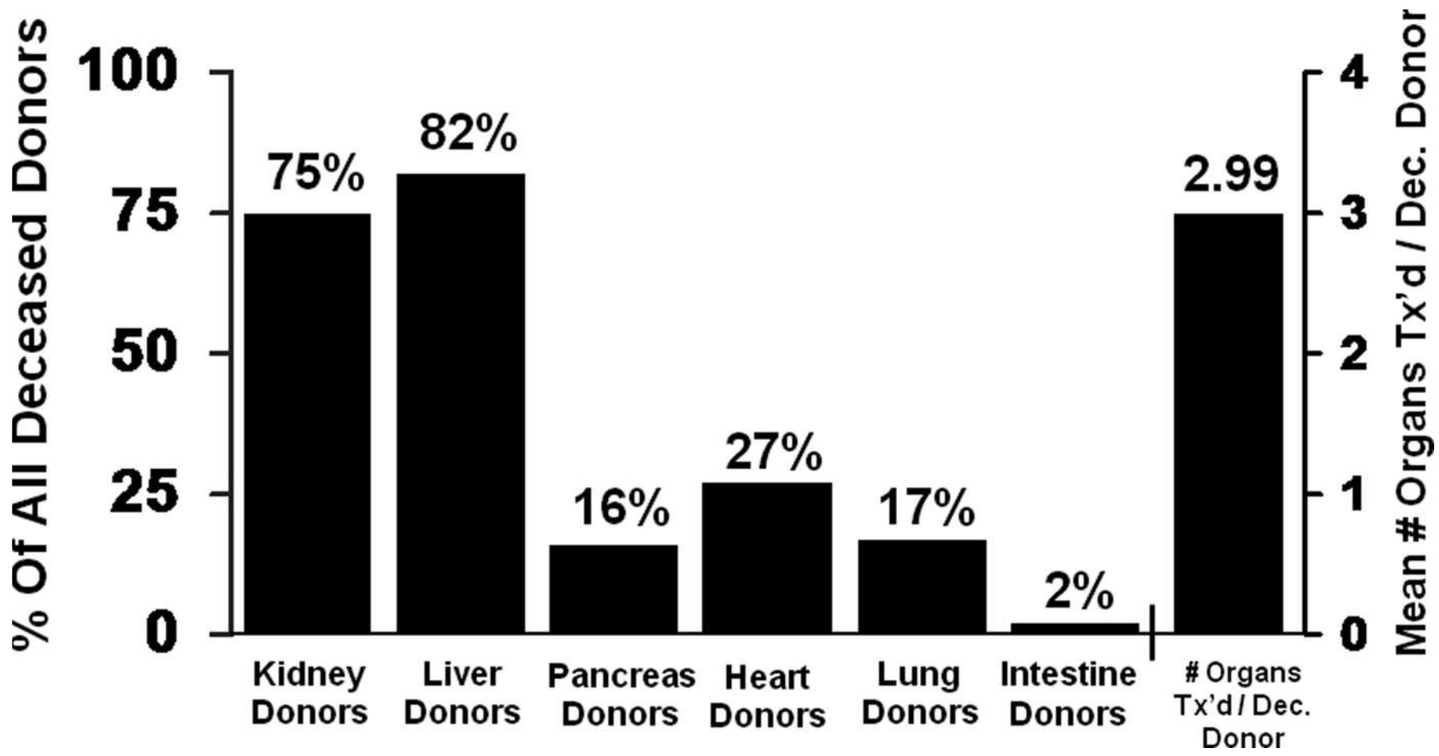

FIGURE 185.2. Organ transplantation rates (by organ) from 8,085 deceased donors (100%) in the United States (2007). The last bar represents the mean number of organs transplanted per deceased donor ("organ yield"). Tx'd, transplanted; Dec., deceased. (Based on data from references [1,2].)

facilitate use of older donors with significant aortic atherosclerosis [50]. Organs with anatomic abnormalities (e.g., multiple renal arteries or ureters, horseshoe kidney, annular pancreas) also are being used routinely. Improvements in operative technique permit the en bloc transplantation of two kidneys from very young donors that would have been too small to be used separately in one recipient [51,52]. Similarly, transplantation of both kidneys from an *adult* donor into one recipient is done to avoid discarding suboptimal kidneys with an insufficient individual nephron mass. To maximize the use of livers, adult donor livers can be split and the two size-reduced grafts transplanted into two recipients (e.g., a pediatric and an adult recipient). A similar principle has also been proposed for the pancreas and has been reported on at least one occasion [53].

Explanted livers from patients undergoing liver transplantation for hepatic metabolic disorders that cause systemic disease without affecting other liver functions (e.g., familial amyloidotic polyneuropathy, hereditary oxalosis) can be used for transplanting other patients ("domino transplant") who are not candidates for deceased livers because of graft shortage (e.g., cirrhotic patients with hepatocellular carcinoma confined to the liver who are not in the group with good expected survival) [54]. The combination of split-liver and domino transplantation can even result in transplantation of three adult patients with one deceased donor graft [55].

The advent of single-lung transplants has made it possible to distribute the heart and lungs of one donor to three recipients. Formerly, transplanting a heart–lung bloc into one recipient was the treatment of choice for end-stage pulmonary disease. If the native heart of a heart–lung recipient is healthy, a domino transplant can be performed: The heart–lung recipient donates his or her heart to another patient in need of a heart transplant. Again, as an attempt to optimize use of scarce donor resources, the reuse of transplanted hearts, kidneys, and livers has been reported [56]. However, all these methods allow only for better use of organs from the existing donor pool. The cornerstone for an effective increase in the number of organ donors remains heightened awareness and education of the public, physicians, and other health care professionals to improve consent and conversion rates [11–13,24,29].

Living Donors

The use of living donors, traditionally limited to kidney transplants, has been expanded to the pancreas, liver, small bowel, and lung [1,2]. In the past, most living donors were genetically related to the recipient—siblings, parents, and adult children. The use of living unrelated kidney donors, who are either emotionally related to the recipient (e.g., spouses, close friends), or emotionally unrelated to the recipient (nondirected, "altruistic" donors) has considerably increased over the past 15 years as a result of the organ shortage [1,2]. In 2008, the 5,968 live donor kidney transplants constituted 34% of all kidney transplants that were done that year [1] (Fig. 185.1). In order to increase that proportion even further, paired-kidney-exchange programs and living donor chain transplants have been implemented [57,58]. In that setting, the supply of organs is increased for instance by exchanging kidneys from living donors who are ABO or cross-match incompatible with their intended recipients, but ABO or cross-match compatible with another donor-recipient pair [donor A would provide a kidney to (ABO or cross-match compatible) recipient B, and donor B would provide a kidney to (ABO or cross-match compatible) recipient A] [57,58]. In cases when paired kidney exchange or donor chain transplants are not available or feasible, it is alternatively possible to precondition the intended recipient of an ABO or cross-match incompatible kidney (by use of plasmapheresis and/or intravenous immunoglobulin and pharmacologic intervention) to still facilitate a successful living donor kidney transplant.

Currently, there is considerable public debate on providing incentives for living kidney donation [59–62]. The debate centers on concerns that reimbursement might lead to the commercialization of organ donation, with the inherent risk of turning potential donors and transplantable organs into a commodity [60–62]. In the United States, those in support of compensating live donors stress that an OPTN-run transparent system of paid living donation would ensure that donors are compensated fairly, eliminate transplant tourism to other countries, greatly diminish the currently existing black market for organs in those countries, and emphasize any potentially interested donor's autonomy—while increasing the organ supply [59,60]. In any case, paid living donation, while a reality in certain regions of the world, remains currently unlawful in the United States and most, if not all, Western Countries.

Even when assuming that (i) public attitudes toward living donation will continue to evolve favorably (Fig. 185.1), (ii) innovative approaches as described above will be increasingly used, and (iii) other alternative means for finding living donors, such as donor solicitation via the internet would ultimately be fully embraced by the transplant community and society, only modest increases of the absolute number of living donors could be expected [60,61,63–66]. Compared with renal transplantation, the proportion of living donor transplants for extrarenal organs is much smaller (less than 5% for liver and less than 0.5% for pancreas, lung, and small bowel) [1]. Thus, living donor transplants will continue to help alleviate the organ shortage for certain organs (kidney, liver) to some extent, but will never be able to completely compensate, even under the best circumstances, for the severe lack of deceased donors.

Other Human Donor Organ Sources

The potential for financial compensation or other rewards for deceased donor families (e.g., compensation for funeral expenses) has been considered as a means to increase donation rates [66].

Certain countries (e.g., China) use organs from executed prisoners. Use of this group would contribute only very small numbers of donors in the United States, and this concept has been rejected by the transplant community here [67]. Likewise, the use of anencephalic babies for solid-organ transplantation would not significantly alleviate the organ shortage because only a few babies fulfill all brain-death criteria. Proposals to use organs from executed prisoners or anencephalic babies would engender a very passionate, emotional debate that could have a negative impact on public opinion and thereby decrease overall organ availability [68]. Therefore, these options are not being actively explored.

Xenotransplantation

Xenotransplantation of organs and tissues from animals into humans offers a potentially unlimited supply of donors [69]. Several attempts have received significant public attention [70], but numerous practical problems remain before this procedure could become clinical reality. Ethical concerns regarding the use of animal organs for transplantation have also been raised [71]. Immunologic concerns include hyperacute rejection (mediated by circulating, preformed natural antibodies), which occurs in vascularized solid-organ transplantation between virtually all discordant species. Also, the biocompatibility of protein synthesized by an animal liver and the human organism is not fully established, and infectious diseases (e.g., caused by retroviruses) could be transmitted using nonhuman primates or pigs

as donors. Genetic engineering of animals before their use as donors to overcome the immunologic barriers is an area of intensive investigation. Significant experimental progress in this area could fundamentally change the field of organ transplantation.

Presumed Consent Laws

Presumed consent laws have been implemented in many areas of the world, most notably in several countries in Europe. These laws permit organ procurement unless the potential donor has objected explicitly. A permanently and easily accessible registry of objectors is a prerequisite for such a system. Emphasis is placed on an individual's decision, and family input is limited. In the United States, presumed-consent legislation does not have broad support, and it is uncertain whether the public could reach a consensus on this issue. Moreover, presumed consent would not alleviate the problem of insufficient donor identification and referral [12].

The beneficial impact that such laws can have became evident in Spain. In that country, presumed consent laws coupled with the creation of a decentralized network of mostly hospital-based, specifically trained transplant coordinators (most of them physicians in intensive care units) in the early 1990s led not only to more efficient identification of eligible deceased donors but also to higher consent rates. Accordingly, the annual donation rate in Spain rose from 14.3 donors per million population (pmp) in 1989 to 34.2 pmp in 2008 (United States, 2008: 26.3 pmp) [72–74]. Interestingly, a similar approach (without the presumed consent component) using in-house coordinators at some hospitals the United States did yield greater consent and conversion rates, too, and underscored the advantages that such a system could have, if implemented at a larger scale [75].

REGULATION AND ORGANIZATION OF ORGAN RETRIEVAL AND ALLOCATION

In the early 1980s, the introduction of new immunosuppressive agents engendered a rise in organ transplant activity. Tissue matching (e.g., by use of living-related donor-recipient combinations) became less important, and the use of brain-dead donors increased (Fig. 185.1). In the wake of these developments, consolidation and national regulation of the organ-sharing and allocation organizations, which had previously functioned mainly at a local and regional level, became necessary.

In the United States, the National Organ Transplant Act (NOTA) of 1984 called for a national system to ensure equitable access to transplant therapy for all patients, a major component of which was fair organ allocation. The federal government commissioned a task force on organ transplantation to define such an allocation system. This task force, whose members were appointed by the U.S. Department of Health and Human Services, resolved that human organs are a "national resource to be used for public good" and recommended the creation of a national Organ Procurement and Transplantation Network (OPTN) [3]. In 1986, the U.S. Department of Health and Human Services awarded the OPTN contract to the United Network for Organ Sharing (UNOS). Pursuant to the contract, UNOS was asked to design a network to achieve balance in the goals of equity in organ access and distribution and in optimal medical outcome [76]. In 1986, the Omnibus Budget Reconciliation Act mandated that only hospital members of the OPTN could perform Medicare- and Medicaid-reimbursed transplant procedures. In 1988, the Organ Transplant Amendments reaffirmed the federal interest in equitable organ allocation by locating authority in UNOS as opposed to local transplant organizations.

The national OPTN is currently still operated by the nonprofit UNOS and is accountable to the U.S. Department of Health and Human Services. All patients on waiting lists of a transplant program are registered with UNOS, which maintains a centralized computer system linking all OPOs and transplant centers. The United States has been divided into 11 regions for organ procurement, allocation, and sharing purposes (Fig. 185.3). Organs are registered, shared, and allocated through use of the central UNOS computer, which generates a list of recipients for each available organ. Patients awaiting deceased transplantation are ranked according to UNOS policies, based on medical and scientific criteria such as blood type, tissue type, length of time waiting on the list, age (pediatric vs. adult), level of presensitization (percentage of panel reactive antibody), and medical status. National sharing of 0-antigen (A, B, and DR HLA loci) mismatched kidneys is mandated. In

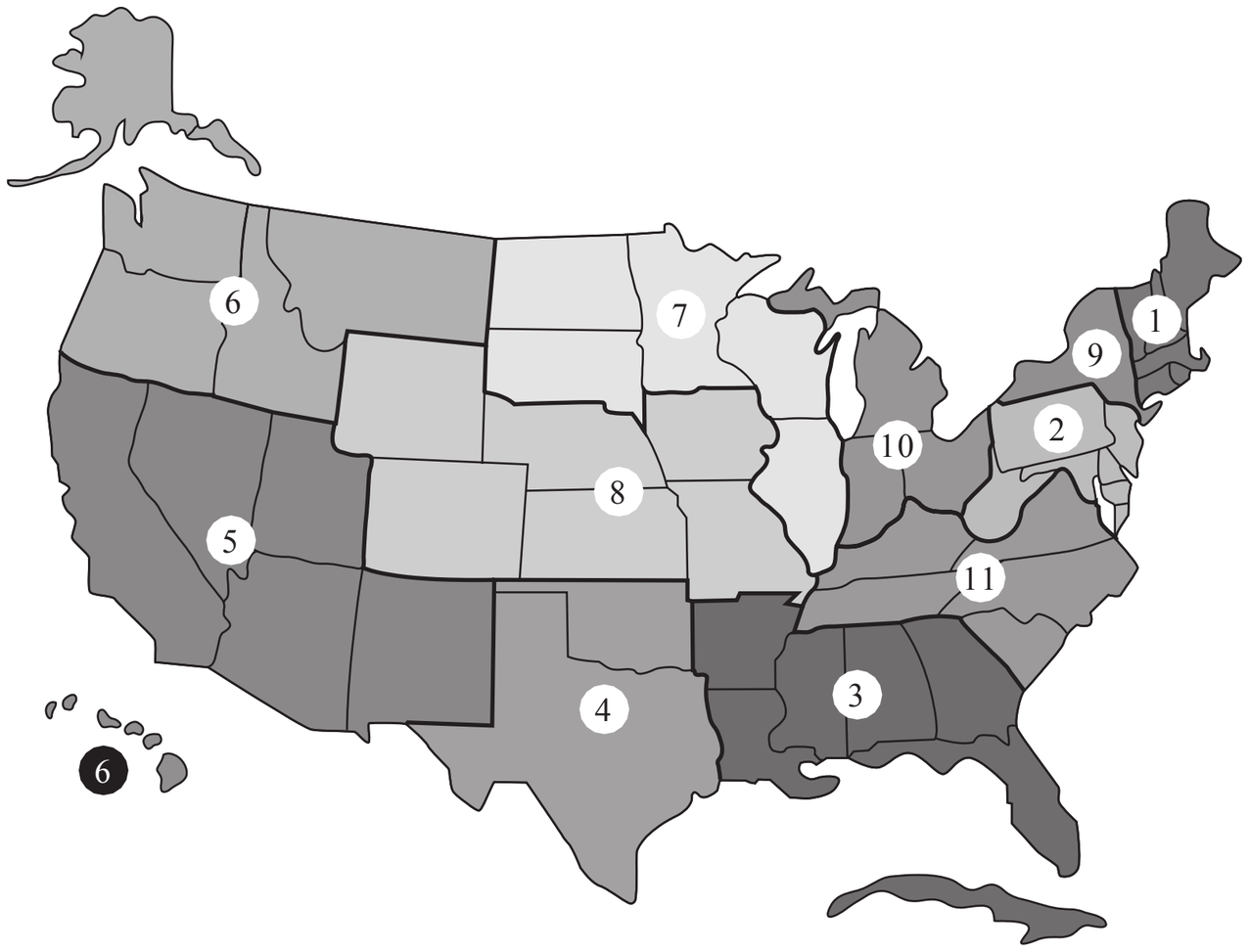

FIGURE 185.3. United Network for Organ Sharing (UNOS) regions in the United States (24-hour access number: 1-800-292-9537). The United States has been divided into 11 regions for organ procurement, allocation, and sharing purposes.

all other cases, and for all other organs, allocation first takes place locally. If no suitable local recipients are available, organs are allocated regionally or nationally [1,76].

LEGAL ASPECTS OF ORGAN DONATION AND BRAIN DEATH

Uniform Anatomical Gift Act

The Uniform Anatomical Gift Act, adopted in 1968 and in force throughout the United States, allows any adult individual (over age 18 years) to donate all or part of the body for transplantation, research, or education. That act provides also the legal basis for procurement of organs from both DCD and brain-dead (vide infra) donors. Explicit consent, which can be revoked at any time, is required. The act also permits legal next of kin to give consent for donation [77]. Donor cards or driver's licenses, on which individuals indicate their consent to postmortem organ donation, are promoted by many states but are legally nonbinding and thus serve ultimately only as a tool to heighten public awareness. In most instances, consent from the next of kin is still sought. Therefore, educational efforts must urge potential donors to make their wishes known to their next of kin [11,13].

Uniform Determination of Death Act

Over the past four decades, brain death has legally become equated with death in most Western developed countries. *Brain death* means that all brain and brainstem function has irreversibly ceased, and circulatory and ventilatory functions are maintained temporarily. The recognition of brain death became possible only after substantial advances in intensive care medicine (e.g., cardiovascular support, prolonged mechanical ventilation). The first classic description of brain death was published in 1959 in France and termed *coma dépassé* (beyond coma). An ad hoc commission of the Harvard Medical School defined brain-death criteria in the United States in 1968 [78]. These criteria were judged by some as being too extensive and too exclusive. In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research formulated the Uniform Determination of Death Act, which established a common ground for statutory and judicial law related to the diagnosis of brain death. The commission stated that "an individual who has sustained... irreversible cessation of all functions of the entire brain, including the brainstem, is dead," and left the criteria for diagnosis to be determined by "accepted medical standards."

Those standards were defined in a related report to the President's Commission on the diagnosis of death by 56 medical consultants in 1981 [79]. The guidelines in that report have now been accepted as the standard for determining brain death in the United States. They are as follows: "Cessation is recognized when (1) all cerebral functions and (2) all brainstem functions are absent. The irreversibility is recognized when (1) the cause of the coma is established and is sufficient to account for the loss of brain functions, (2) the possibility of the recovery of any brain functions is excluded, and (3) the cessation of cerebral and brainstem function persists for an appropriate period of observation and/or trial of therapy" [79]. Confusion regarding this well-founded and accepted medicolegal concept of the equivalence of brain death and death of a human persists to this date among physicians, other health care professionals, and the general public [11,13]. Specifically, in the field of transplantation, it should be unequivocally clear to the potential donor's family and anyone involved in the patient's care that the time of death is the time at which the diagnosis of brain death is established and not the time of cardiac arrest during the organ retrieval. Providing education targeted specifically at these groups and society at large is of paramount importance to optimize consent rates [11,13].

Required Request

Required request laws have now been enacted in all states in the United States. They obligate hospitals to notify an OPO of potential donors and to offer the option of donation to the families of potential donors (brain-dead or DCD donors).

Clinical Diagnosis of Brain Death

The clinical diagnosis of brain death rests on three criteria: (a) irreversibility of the neurologic insult, (b) absence of clinical evidence of cerebral function, and, most important, (c) absence of clinical evidence of brainstem function [79–81] (Table 185.4). Irreversibility is established if structural disease (e.g., trauma, intracranial hemorrhage) or an irreversible metabolic cause is known to have occurred. Hypothermia, medication side effects, drug overdose, or intoxication need to be ruled out when testing for brain death. Plasma concentrations of sedative or analgesic drugs sometimes correlate poorly with cerebral effects. Therefore, residual effects of those drugs can be excluded only by passage of time, if any doubts exist. The observation period (the waiting time between two sequential brain-death examinations) should be at least 6 hours for structural causes and preferably 12 to 24 hours for metabolic causes, drug overdose, or intoxication [80]. Even with potentially reversible metabolic alterations (e.g., hepatic or uremic encephalopathy), recovery has not been described after duration of the brain-death state for more than 12 hours. Clinical testing of cerebral and brainstem function is detailed in Table 185.4 [79–82]. It should be noted that brain-death criteria are more stringent for very young pediatric patients, particularly newborns, in whom criteria for brain death also include demonstration of the absence of blood flow on cerebral flow studies.

After brain death, the pupils become fixed in midposition because sympathetic and parasympathetic input is lost. Decerebrate (abnormal extension) and decorticate (abnormal flexion) responses to painful stimuli imply the presence of some brainstem function and are incompatible with the diagnosis of brain death. In contrast, spinal cord–mediated tendon reflexes, automatic stepping, and other spinal cord–generated movements (which can occur during apnea testing) are compatible with the presence of brain death [83]. The occurrence of these movements can be quite distressing if observed by the next of kin; therefore, it is advisable that they not be present during the apnea test. Very rarely, ascending acute reversible inflammatory polyneuropathy (Guillain–Barré syndrome) can simulate brain death and inhibit all motor functions, including pupillary reactions and brainstem reflexes. The typical clinical history, coupled with evidence of progressive weakness, yields the correct diagnosis and precludes a diagnosis of brain death being established [80].

The American Academy of Neurology has stated that special confirmatory tests are not necessary to diagnose brain death in the vast majority of cases. Only in equivocal or questionable circumstances do tests demonstrating absence of intracranial blood flow or the presence of an isoelectric electroencephalogram need to be performed [80,81]. The most sensitive and specific test for assessing intracranial blood flow is four-vessel cerebral arteriography. All other adjunctive tests are

TABLE 185.4

BRAIN DEATH CRITERIA AND CLINICAL DIAGNOSIS OF BRAIN DEATH

Irreversible, well-defined etiology of unconsciousness
Structural disease or metabolic cause
Exclusion of hypothermia; hypotension; severe electrolyte, endocrine, or acid-base disturbance; and drug or substance intoxication
Sufficient observation period (at least 6 h) between two brain death examinations
No clinical evidence of cerebral function
No spontaneous movement, eye opening, or movement or response after auditory, verbal, or visual commands
No movement elicited by painful stimuli to the face and trunk (e.g., sternal rub, pinching of a nipple, or fingernail bed) other than spinal cord reflex movements
No clinical evidence of brainstem function
No pupillary reflex: pupils are fixed and midposition; no change of pupil size in either eye after shining a strong light source in each eye sequentially in a dark room
No corneal reflex: no eyelid movement after touching the cornea (not the conjunctiva) with a sterile cotton swab or tissue
No gag reflex: no retching or movement of the uvula after touching the back of the pharynx with a tongue depressor or after moving the endotracheal tube
No cough reflex: no coughing with deep tracheal irrigation and suctioning
No oculocephalic reflex (doll's eyes reflex): no eye movement in response to brisk turning of the head from side to side with the head of the supine patient elevated 30 degrees
No oculovestibular reflex (caloric reflex): no eye movements within 3 min after removing earwax and irrigating each tympanic membrane (if intact) sequentially with 50 mL ice water for 30 to 45 seconds while the head of the supine patient is elevated 30 degrees
No integrated motor response to pain: no localizing or withdrawal response, no extensor or flexor posturing
No respiratory efforts on apnea testing ($PaCO_2$ > 60 mm Hg or 20 mm Hg higher than the normal baseline value): The patient is preoxygenated with an FIO_2 of 1.0 for 10–15 min, preferably with an arterial line in place for rapid blood gas measurements, while adjusting ventilatory rate and volume such that the $PaCO_2$ reaches □40–45 mm Hg. After a baseline arterial blood gas value is obtained and the patient is disconnected from the ventilator, O_2 at 6–8 L/min is delivered through a cannula advanced 20–30 cm into the endotracheal tube (cannula tip at the carina). Continuous pulse oximetry is used for early detection of desaturation, which does not usually occur when using this protocol. In most cases, a $PaCO_2$ > 60 mm Hg is achieved within 3–5 minutes after withdrawal of ventilatory support; at this point, the patient should be reconnected to the ventilator (or earlier, should hemodynamic instability, desaturation, or spontaneous breathing movements occur). Obtaining an arterial blood gas sample immediately before reinstitution of mechanical ventilation is mandatory. If there is no evidence of spontaneous respirations before reinstitution of mechanical ventilation in the presence of a $PaCO_2$ > 60 mm Hg or an increase of > 20 mm Hg from the normal baseline value, the criteria for a positive apnea test are met.
Other points
Spinal reflexes, such as deep tendon reflexes and triple flexion responses, can be preserved and do not exclude the diagnosis of brain death
Shivering, goose bumps, arm movements, reaching of the hands toward the neck, forced exhalation, and thoracic respiratory-like movements are possible after brain death and are likely due to neuronal impulse release phenomena of the spinal cord, including the upper cervical cord. All these findings are compatible with the diagnosis of brain death.
Confirmatory tests should be used in cases in which the observation period needs to be shortened (e.g., unstable donors), in equivocal situations in children younger than 1 year old, or if one of the potential pitfalls (Table 185.6) cannot be ruled out (demonstration of absence of intracranial circulation by angiographic contrast or radioisotopic flow studies, transcranial Doppler ultrasonography, or electrocerebral silence documented by an electroencephalogram).

$PaCO_2$, partial arterial carbon dioxide pressure; FIO_2, fraction of inspired oxygen.
From references [79–82].

less sensitive (e.g., digital subtraction angiography, transcranial Doppler ultrasonography), are less specific (e.g., brainstem acoustic evoked potentials), measure only hemispheric flow (e.g., radioisotope angiography), or are indirect (e.g., computed tomography, echoencephalography). If either hemispheric neuronal function (electroencephalogram) or hemispheric flow is assessed, reliable clinical testing of the brainstem must be performed to confirm the diagnosis. The use of a brain-imaging modality, positron emission tomography (using ^{18}F-fluorodeoxyglucose to assess brain metabolism), to diagnose brain death is currently not universally recommended [80]. The decision whether to accept ^{18}F-fluorodeoxyglucose–positron emission tomography as a confirmatory test for determination of brain death is awaiting the results of further studies.

Four-vessel cerebral arteriography is indicated in all conditions that can temporarily cause an isoelectric electroencephalogram (e.g., extreme intoxication). If the indication for cerebral arteriography is unclear, the benefits must be weighed against the potential risks of transporting an unstable patient, hypotension after contrast injection, and the nephrotoxic effects of injection of contrast media that potentially may affect early renal allograft function [82]. Confirmatory tests may serve to shorten the waiting period between the two brain-death examinations, should donor hemodynamic instability occur. Certain potential pitfalls exist in clinical brain-death testing, and the diagnosis should not be considered to have been established until these all have been excluded (Table 185.5). If these cannot be excluded, confirmatory testing is mandatory [80,81].

In summary, the diagnosis of brain death can be established by performance of routine neurologic examinations, including cold caloric and apnea testing on two separate occasions,

TABLE 185.5

PITFALLS IN CLINICAL BRAIN DEATH TESTING AND POTENTIAL REMEDIAL MEASURES[a]

Pitfalls	Remedial measure(s)
Hypotension, shock	Institute fluid resuscitation, use of pressor agents
Hypothermia	Use warmed fluids, ventilatory warmer
Intoxication or drug overdose	If measurable, check drug levels and toxicology screens or increase waiting time between brain death examinations
Neuromuscular and sedative drugs, which can interfere with elicitation of motor responses	Discontinue muscle relaxants and mood- or consciousness-altering medications, increase waiting time between brain death examinations
Pupillary fixation, which may be caused by anticholinergic drugs (e.g., atropine given during a cardiac arrest), neuromuscular blocking agents, or preexisting disease	Discontinue anticholinergic medications and muscle relaxants, increase waiting time between brain death examinations, obtain careful patient history
Corneal reflexes absent due to overlooked contact lenses	Remove contact lenses before brain death examination
Oculovestibular reflexes diminished or abolished after prior use of ototoxic drugs (e.g., aminoglycosides, loop diuretics, vancomycin) or agents with suppressive side effects on the vestibular system (e.g., tricyclic antidepressants, anticonvulsants, and barbiturates) or due to preexisting disease	Obtain careful medication history and patient history

[a]If one of the listed conditions cannot be ruled out, confirmatory testing (cerebral flow studies or electroencephalography) is necessary before brain death is declared.

coupled with prior establishment of the underlying diagnosis and prognosis in most cases. More sophisticated tests are required in cases in which the diagnosis cannot be unequivocally established. However, brain death must be diagnosed in accordance with local regulations and state laws. Details on the locally prevailing regulations are available through the state medical board or the local OPO.

ORGAN DONATION PROCESS

The three key elements leading to successful organ donation are (a) early referral of potential donors, (b) a well-coordinated approach in informing and dealing with the potential donor's family to request and obtain consent, and (c) appropriate critical care therapy of the donor [11,13,15,16]. The optimal course of events for both brain-dead and DCD donors is summarized in Table 185.6.

Early Donor Referral

Early referral of any potential donor to the local OPO minimizes the loss of transplantable organs due to unexpected cardiac arrest and death, hemodynamic instability, serious nosocomial infection, or complications related to intensive care [16,84,85]. For example, an inverse correlation exists between the duration of mechanical ventilation and the suitability of the donor for lung donation.

The evidence is substantial that brain death eventually leads to cardiac arrest, even when cardiorespiratory support is maintained [84,86]. Cardiac arrest occurs in 4% to 28% of potential donors in the maintenance phase. Although approximately 50% of all potential donors die within 24 hours without appropriate support, as many as 25% are not recognized for 48 hours or longer, with identification occurring only at the time of cardiovascular death [86].

The previously outlined clinical guidelines for referral to the local OPO should be applied to any neurologically severely injured patient after admission to the hospital or intensive care unit (Table 185.3). Early contact with the OPO is essential as the latter will provide assistance with further screening and the evaluation of any patient who might potentially become a donor.

Donor Evaluation

General Guidelines

During the initial contact with the OPO, the physician should provide the potential donor's name, age, sex, height, weight, and blood type. Also needed are the date of admission and diagnosis, the nature and extent of any trauma, a concise medical and social history, and the time of brain death (if applicable). Whether local investigative agencies (e.g., medical examiner, coroner) need to be notified also should be specified. The current medical status, including vital signs, urine output, cardiorespiratory status, medications, and culture results, must be communicated. Basic laboratory results should be obtained: arterial blood gas determinations; blood urea nitrogen, creatinine, and electrolyte values; hemoglobin, hematocrit, white blood cell and platelet counts, and tests for serum amylase, total bilirubin, alkaline phosphatase, alanine aminotransferase,

TABLE 185.6

ORGAN DONATION ALGORITHM[a]

1. Early identification of the potential donor by the critical care physician or health care professional (Table 185.3)
2. Early contact with the local or regional OPO for medical, legal, and logistic assistance. If the local OPO's address or phone number is unknown, a 24-h access number to UNOS is available: 1–800-292–9537.
3. Completion of the preliminary screening by the OPO if necessary in consultation with the transplant surgeon for decisions regarding marginal donors

4a. For potential DCD donors: await family decision regarding withdrawal of care. Proceed only if family decides to do so.

4b. For potential brain-dead donors: brain death diagnosis and confirmation (Tables 185.4 and 185.5), certification of death. Family notification and explanation of brain death with its legal and medical implications. Sufficient time for acceptance must be allowed.

5. Request for organ donation. Must be made after, in clear temporal separation, from step 4a or 4b.
6. After consent for organ donation is obtained, the focus switches from treatment of elevated intracranial pressure and cerebral protection to preservation of organ function and optimization of peripheral oxygen delivery (Table 185.8).
7. All remaining laboratory and serologic studies as well as any further studies and tests required in equivocal situations are performed at this point (e.g., coronary angiography for older or marginal heart donors).
8. Final organ allocation by the OPO and UNOS, coordination of the organ recovery operation, notification of the abdominal and thoracic surgical teams. Modification of the final steps may become necessary under special circumstances, for example, in hemodynamically unstable donors.
9. For DCD donors: Support is withdrawn and death is certified (in the ICU or in the operating room).
10. Organ recovery operation (brain-dead and DCD donors).

[a]Steps 4, 5, and 9 should not involve physicians who are part of the transplantation team.
OPO, organ procurement organization; UNOS, United Network for Organ Sharing; DCD, donation after cardiac death.

and aspartate aminotransferase; coagulation profile (including prothrombin time or International Normalized Ratio [INR]); and urinalysis and urine culture should be available, along with electrocardiogram and chest radiograph results. In the case of potential lung donors, chest circumference and radiographic thoracic measurements, as well as the results of an oxygenation challenge [partial arterial oxygen pressure (PaO_2) measurement after ventilation for 10 minutes with a fraction of inspired oxygen (FIO_2) of 1.0], are helpful.

The OPO provides further procedural, administrative, legal, and logistic help. Most importantly, the OPO coordinates how the family is approached. All further testing [including HLA-tissue typing; serologic screening for cytomegalovirus (CMV), for hepatitis A, B, and C viruses, for human immunodeficiency virus (HIV), and for human T-cell lymphotropic virus type I and syphilis; and blood, sputum, and urine cultures] is then coordinated through the OPO if the donor passes the preliminary screening tests. The organ allocation process begins only after the family has decided to withdraw support (DCD donors) or brain death has been declared and consent has been obtained. If prospective tissue typing is to be done, performing a surgical inguinal lymph node biopsy at the donor hospital may be necessary—after consent for organ donation has been obtained but before proceeding with the actual organ recovery several hours later.

The medical status and the life expectancy of the potential recipient without the organ transplant are taken into account when the final decision about transplantation of a specific donor organ is made. The ultimate decision regarding the use of a donor organ is made by the transplant surgeon. At this point, the transplant center may need to obtain further tests to assess the functional status of one or more organ systems. For example, if the heart is to be retrieved, an echocardiogram is usually obtained. In selected donors, coronary angiography is performed. Pulmonary status can be further assessed by bronchoscopy after considering the results of the chest radiograph, oxygenation challenge, and sputum cultures. For potential liver donors who might have fatty liver disease, a percutaneous bedside liver biopsy can be performed. If concern over the suitability of organs arises, direct inspection by the transplant surgeon is necessary at the time of the organ procurement operation. In some cases, an open biopsy (e.g., for kidney or liver) and frozen section pathologic analysis obtained at the time of organ recovery also help in the final decision making. Direct inspection also is important in organ donors who suffered a blunt injury to the head and trunk (e.g., motor vehicle accident). Under these circumstances, intra-abdominal organs have been used successfully despite the presence of parenchymal tears or subcapsular hematomas in either the liver or kidney. Significant injuries to the pancreas preclude its use.

In summary, *each* patient with a severe neurologic injury should be referred to the local OPO as a potential donor, regardless of type of brain injury (e.g., trauma, stroke), history, age, or medical condition (Table 185.3). With few exceptions (vide infra), organ donation should never be excluded a priori because of the clinical situation, the results of imaging studies, or the magnitude of an injury, without first having contacted the local OPO (24-hour access number: 1–800-292–9537).

Organ-Specific Considerations

The use of kidneys from older donors, donors dying of cardiovascular disease, or donors requiring large doses of inotropic drugs for cardiovascular support entails a higher rate of delayed or diminished graft function and is associated with decreased graft survival [87,88]. Nevertheless, organs from these so-called marginal donors are routinely used, given the current prolonged periods (greater than 6 years) that some recipients may wait for available organs, during which their medical condition may deteriorate. Marginal donor kidneys benefit from preservation on a pulsatile perfusion pump, which was shown to improve quality of early graft function and long-term outcomes [44]. In equivocal cases (e.g., donors with elevated baseline serum creatinine levels or a history of hypertension), renal biopsies at the time of organ recovery may quantify the amount of preexisting donor arteriosclerosis or glomerulosclerosis. The critical shortage of organs has led to increasing relaxation of exclusion criteria, with satisfactory long-term results in many recipients. Donor organ function is more important than donor biologic age.

Livers from donors with an abnormal liver enzyme or coagulation profile can frequently still be transplanted. Elevated hepatic enzyme levels may reflect transient hepatic ischemia at the time of resuscitation. The trends observed in the results of serial hepatic enzyme levels are more important than absolute values. Abnormal coagulation test results may be due to disseminated intravascular coagulation (commonly a result

of brain injury, not primary hepatic dysfunction). Significant donor hypernatremia (e.g., > 155 mg per dL), as commonly observed in under resuscitated brain-dead donors with significant diabetes insipidus, is a risk factor for primary liver graft nonfunction posttransplant. Aggressive intervention prior to procurement is warranted and will ultimately allow for safe transplantation of liver grafts from these hypernatremic donors. The decision to use a liver from a marginal donor has to be made on the basis of relatively crude information. Often, only direct inspection, with or without a biopsy of the liver, at the time of organ recovery provides a final answer and may be the only way to assess a donor with a history of significant ethanol intake. Severe hepatic steatosis is one of the most significant factors predictive of early posttransplant hepatic dysfunction or failure.

In general, donors older than 55 years of age are not considered for pancreas donation. However, donors with hyperglycemia [caused by peripheral insulin resistance, particularly after brain death (see "Endocrine Therapy" section) or hyperamylasemia (which can be a consequence of severe head injury without actual pancreatitis)] [89] are not to be excluded a priori from pancreas donation, because these factors do not necessarily influence posttransplant outcome [90]. A pancreas transplant registry analysis suggested a slightly higher incidence of graft thrombosis for pancreata that had been procured from donors treated with desmopressin (vs. those that did not) [91]. Clearly, further study is necessary to confirm or refute these findings and determine their clinical significance. Currently, the only absolute contraindications to pancreas donation are a history of impaired glucose tolerance or insulin-dependent diabetes mellitus, direct blunt or penetrating trauma to the pancreas, or the finding of acute or chronic pancreatitis at the time of the donor operation.

Regarding heart donation, an important criterion is good donor heart ventricular function immediately before retrieval, as judged by the cardiac surgeon at visual inspection during organ recovery. Ideally, no potential heart donor should be excluded solely on the basis of echocardiographic wall motion abnormalities, a borderline or abnormal ejection fraction, inotropic medication requirements, or heart murmurs, arrhythmias, or other electrocardiographic changes (which often occur in brain-dead individuals in whom no cardiac disease is present) [16].

Risk factors associated with poorer outcome after lung transplantation include a history of smoking, aspiration, purulent secretions observed during bronchoscopy, an abnormal chest radiograph, or an unsatisfactory oxygenation challenge (PaO_2 less than 300 mm Hg after 10 minutes of ventilation with FIO_2 of 1.0 and PEEP of 5 cm H_2O) alone or in combination in lung donors. However, even lungs obtained from such marginal donors have been successfully transplanted [92]. Bronchoscopy often is performed as a final confirmatory test in the operating room by the transplant surgeon immediately before retrieval. Direct intraoperative inspection of the lungs determines whether significant contusions are present, which could preclude use of the organs.

In conclusion, the traditional donor criteria have been considerably expanded over recent years, for both thoracic and abdominal organs, due to the ongoing, severe donor shortage.

Transmission of Infectious Diseases

Transmission of bacterial or fungal infection through organ transplantation can be due to contamination of the organ itself during organ procurement or storage. Published evidence suggests that organs transplanted from bacteremic donors do not transmit bacterial infection or result in poorer recipient outcomes [93]. However, potential donors who exhibit or develop active bacterial or fungal infection that is unresponsive to adequate source control and antibiotic therapy or who have evidence of severe systemic sepsis with positive blood cultures (even without a primary source) should be rejected. Similarly, active tuberculosis is a contraindication to organ donation. Positive urine cultures do not preclude renal donation. Donors with serologic evidence of syphilis have been successfully used.

Absolute contraindications to donation include evidence of significant *acute* viral infections (e.g., viral encephalitis, systemic herpes simplex virus infections, acute viral hepatitis A, B, or C), seropositivity for HIV, and the acquired immunodeficiency syndrome. Individuals known to be at high risk for acquiring such diseases (e.g., intravenous [IV] drug users, prostitutes, or residents of sub-Saharan Africa) are only accepted as donors on a case-by-case basis.

Potential donors that test positive for the hepatitis B virus (HBV) surface antigen (HBsAg) or HBe antigen are usually precluded from donating [16,94]. Serologic positivity for the hepatitis B core antigen antibody (HBcAb) does not constitute an absolute contraindication to proceed with donation [94]. Acceptable organs from donors with any type of serologic evidence of HBV are usually only transplanted into recipients that have demonstrated immunity against HBV (i.e., HBsAb-positivity). Selected recipients may also receive HBV immunoglobulin or lamivudine, or both, beginning at the time of transplant [94]. Ideally, however, all potential organ transplant recipients should receive HBV immunization during the pretransplant evaluation [16].

The use of hepatitis C (HCV)–seropositive donors for selected recipients has become routine [16,95]. For adequate identification of HCV-positive donors, many OPOs now routinely perform nucleic acid testing (by polymerase chain reaction [PCR]) for HCV–RNA. HCV-infected livers and kidneys transplanted into HCV-infected recipients do not convey a worse outcome than HCV-negative grafts [16,95]. In essence, exclusion of all HCV-positive donors would increase the organ shortage while preventing what would appear to be relatively limited disease transmission. As is the case for HBV serology–positive donors, the final decision regarding the use of an HCV serology–positive donor must be made on an individual basis by each transplant surgeon. Factors that are taken into account in such circumstances include the likelihood of disease transmission, the recipient's current medical and serologic status, and whether the organ to be transplanted is life-saving (e.g., liver, heart) [16,95].

CMV also can be transmitted by donor tissue, particularly to CMV-seronegative patients. Effective prophylaxis against and treatment of CMV disease have become a reality with the advent of effective antiviral agents such as ganciclovir and valganciclovir. Positive CMV serologies do not preclude organ donation but have been used to identify high-risk donor-recipient combinations (CMV-seropositive donor–CMV-seronegative recipient) where prophylaxis should be used and careful surveillance for CMV disease is important.

Transmission of Malignancy

Transmission of malignancy via donor organs is very rare [16]. Because donor selection is particularly important in this regard, donors with most types of cancer should not be used. The exceptions are those with low-grade skin malignancies, such as basal cell carcinoma and most squamous cell carcinomas; carcinoma in situ of the uterine cervix; or primary brain tumors, which rarely spread outside the central nervous system (CNS; e.g., grade I astrocytomas, benign meningiomas, and hemangioblastomas, but not medulloblastomas and glioblastomas) [16,96]. It is important to ensure that a CNS tumor does not represent a focus of metastatic disease from the

primary site. Metastases from choriocarcinomas, bronchial or renal malignancies, and malignant melanomas may present as what appears to be a primary brain tumor or may bleed and be mistaken for an intracranial hemorrhage because of an arteriovenous malformation or a ruptured aneurysm. Previous treatment of a neoplasm, menstrual irregularities after a pregnancy or a spontaneous abortion in women of childbearing age (suggestive of a choriocarcinoma), or evidence of lesions at other sites in the patient with a purported primary CNS malignancy should preclude organ donation. Donors with primary brain tumors should not be used if they have undergone radiotherapy, chemotherapy, ventriculoperitoneal or ventriculoatrial shunting, or craniotomies, because these treatments either are associated with high-grade malignancies or create potential pathways for the systemic dissemination of tumor cells [16,96].

If a potential donor has had successful cancer treatment in the past, the transplant surgeon must weigh the small potential risk of transmitting micrometastases against discarding a potentially life-saving organ. In general, patients with a history of malignancy with little propensity to recur after therapy (e.g., small, noninvasive lesions treated by complete surgical excision) are considered as organ donors, particularly if they have remained without evidence of recurrence for more than 5 years. Patients who have experienced invasive cancer in which a substantial risk of late recurrence exists (e.g., breast cancer, malignant melanoma), particularly if a large lesion was initially present and chemotherapy or radiation therapy was used, should probably not be considered for donation. Similarly, patients with a history of leukemia or lymphoma should not be considered as donors.

Required Request for Organ Donation and Consent

After the OPO determines the suitability of a potential donor, the next important steps are the brain-death examination (when applicable) and the legally required request for organ donation (Table 185.6). Those steps should *not* involve any of the physicians associated with the transplant team, as this would represent a potential conflict of interest. In 1987, federal required-request legislation became effective and has since been adopted by every state in the United States. Required-request laws mandate that the family of a potential organ donor be offered the option of organ donation. The hospital must notify the local OPO of the presence of a potential organ donor. Several studies have shown that consent rates are highest when an OPO coordinator—rather than a member of the patient's ICU team such as a physician or a nurse—approaches the family about organ donation [11–13,75].

Brain-Dead Donors

For brain-dead donors, it is of the utmost importance to ensure that (a) the family understands and accepts the concept of brain death, including its legal and medical equivalence with death; (b) the request for organ donation is *not* made at the same time that brain death is explained (unless the family voiced the wish to consider donation earlier during the hospitalization); and (c) the approach and request be made by an OPO representative (rather than a member of the potential donor's care team). Sufficient time must be given to the next of kin to begin coping with this information and to accept the loss of the family member. Only then, in clear temporal separation from the explanation of death, should the subject of organ donation be broached and an appropriate request be made [11,13]. As a case in point, within one region of the United States, consent rates were 18% when the discussion of death and the request for donation were combined but rose to 65% when these issues were discussed separately [97]. Also, the family must be informed that after declaration of brain death and consenting to organ donation, all hospital costs relating to donation will be paid by the OPO.

DCD Donors

Families of patients with severe, irreversible brain injuries who do not fulfill the formal criteria of brain death might decide to forgo any further life-sustaining treatment. Only then can the subject of organ donation be broached with the family. As discussed earlier, it is paramount that the approach to the family and the request for organ donation be made by an OPO representative [26,98,99].

Consent

Driver's licenses and signed donor cards are not considered legally binding documents for the purpose of organ donation. Thus, the family's wishes under such circumstances are virtually always honored, even if they are contrary to the donor's wishes expressed on a driver's license or donor card. The Uniform Anatomical Gift Act of 1968 specifies the legal next-of-kin priority for donors over age 18 years in the following order: (a) spouse, (b) adult son or daughter, (c) either parent, (d) adult brother or sister, and (d) legal guardian [79]. Similarly, the order of priority for donors under age 18 years is as follows: (a) both parents, (b) one parent (if both parents are not available and no wishes to the contrary of the absent parent are known), (c) the custodial parent (if the parents are divorced or legally separated), and (d) the legal guardian (if there are no parents). In part in response to the aforementioned dilemma, nearly all states in the United States have now created state donor registries where residents can register their decision to donate (usually on-line) to ensure that they can donate their organs [24]. Such initiatives help to relieve families of making an often difficult decision on the donor's behalf. In contrast to driver's licenses and signed donor cards, an individual's decision to donate that is documented in a state donor registry cannot be overridden by the family [24].

PERIOPERATIVE CRITICAL CARE MANAGEMENT OF THE BRAIN-DEAD ORGAN DONOR

Although some of the critical care issues that pertain to brain-dead organ donors have been met by significant clinical and basic research interest (e.g., hormonal changes and hormonal replacement therapy), there is an overall lack of randomized, controlled studies that could lead to a more evidence-based approach to the care of these patients. The level of evidence provided by these studies is mainly low. It is therefore important to acknowledge that some of the following recommendations may undergo substantial revision as additional, new evidence emerges (Tables 185.7 and 185.8).

Pathophysiology of Brain Death

The majority of our knowledge of the pathophysiologic changes during and after brain death has been derived from experiments performed using animal models. Hemodynamic instability during the phase of impending brain herniation is the result of autonomic dysregulation secondary to the progressive

TABLE 185.7

MAINTENANCE THERAPY ENDPOINTS IN THE BRAIN-DEAD ORGAN DONOR

Variable	Therapeutic endpoint
Systolic blood pressure	100–120 mm Hg or mean arterial pressure ≥ 60 mm Hg
Central venous pressure	8–10 mm Hg
Urine output	100–300 mL/h
Core temperature	> 35°C
Partial arterial oxygen pressure	80–100 mm Hg
Systemic arterial oxygen saturation	95%
pH	7.37–7.45
Hemoglobin	10–12 g/d
Hematocrit	30–35%

loss of central neurohumoral regulatory control of vital functions. The continuous increase in intracranial pressure with worsening brain ischemia leads to severe systemic hypertension (Cushing's response) and frequently is associated with tachyarrhythmias. This process is mediated by an increase in sympathetic activity and an excess of circulating catecholamines ("autonomic storm") [100–102]. A brief period of transient bradycardia associated with the hypertensive response can be seen in the early phase of brain herniation (Cushing's reflex).

During the phase of increased sympathetic activity, there is evidence that coronary blood flow is significantly impaired, resulting in cardiac microinfarcts. Furthermore, decreased hepatic perfusion due to increased intrahepatic shunting has been demonstrated as a result of the excessive sympathetic activity. Neurogenic pulmonary edema is thought to develop during the autonomic storm phase secondary to the temporary elevation of left atrial pressures over the level of pulmonary arterial and alveolar capillary pressures. This causes massive transudation of fluid from the microvasculature into the alveoli and interstitial hemorrhage [100–102]. Within approximately 15 minutes after brain herniation and brain death, catecholamines decrease to below baseline values.

The resting vagal tone is abolished because of destruction of the nucleus ambiguus, eliminating all chronotropic effects of atropine administered after brain death. The total carbon dioxide production after brain death is low, because of the absence of cerebral metabolism and the presence of hypothermia and decreased muscle tone. The subsequent chronic maintenance phase of brain-dead donors is frequently characterized by hypotension, resulting mainly from complete arterial and venous vasomotor collapse with significant peripheral venous pooling.

An increasing body of experimental evidence also shows that brain death leads to activation of proinflammatory and immunoregulatory pathways [102–106]. In small animal brain-death models, messenger ribonucleic acid and protein expression within peripheral solid organs were significantly increased for cytokines (e.g., interleukin-1β, interleukin-6, tumor necrosis factor-α, interferon gamma, tumor growth factor-β), chemokines (e.g., RANTES), adhesion molecules (e.g., P- and E-selectin), and vasoconstrictors (e.g., endothelin) [102–106]. Importantly, brain death has also been associated with enhanced expression of immunoregulatory molecules such as major histocompatibility complex class I and II proteins [103]. Consistent with these findings, increased immunogenicity and accelerated rejection were noted in kidneys and hearts transplanted from brain-dead rodents [102].

Routine Care and Monitoring

Regular nursing care must be continued after brain death. Frequent turning to prevent decubitus ulcers, skin care, dressing changes, urinary and intravascular catheter care, and catheter site care must be meticulous to minimize the risk of infection. Other indwelling devices should be removed, if possible (e.g., ventriculostomies and ventriculoatrial or ventriculoperitoneal shunts, which may have been inserted in certain patients for monitoring or treating of elevated intracranial pressure). Any urinary and intravascular catheters that may have been inserted under suboptimal, emergent conditions without appropriate aseptic technique at the time of original injury should be replaced. A nasogastric tube should always be inserted for gastric decompression and prevention of aspiration.

Arterial lines should be inserted preferentially into peripheral arteries of the upper extremities because femoral arterial line readings can become inaccurate from surgical manipulation of the abdominal aorta during organ procurement. Similarly, central venous catheters should not be inserted through the femoral vein because dissection and manipulation of the interior vena cava occur during organ procurement. In addition, venous catheters inserted through the femoral vein can cause iliac vein thrombosis. This increases the risk of pulmonary embolization, particularly during surgical venous dissection. Thrombosis can also render the iliac veins unsuitable for use in vascular reconstruction, which may be necessary for some types of abdominal or thoracic organ transplants.

The following parameters must be determined routinely and frequently for all organ donors using various monitoring devices: core temperature (esophageal, rectal, or indwelling bladder catheter temperature probes), heart rate (continuous electrocardiographic monitoring), systemic blood pressure (arterial catheter), central venous blood pressure (subclavian or internal jugular central venous catheter), arterial oxygen saturation (pulse oximetry), and hourly urine output (Foley catheter). Use of a pulmonary artery catheter for measurement of pulmonary arterial and left ventricular wedge pressure and central venous oximetry is not routinely necessary; its use should be reserved for selected unstable donors whose volume status is uncertain or who exhibit persistent acidosis with evidence of tissue hypoperfusion. Laboratory parameters also must be checked regularly, including arterial blood gas, serum electrolytes, blood urea nitrogen, creatinine, lactate, and liver enzyme values; total bilirubin; and hemoglobin, hematocrit, platelet count, and coagulation tests. Testing is adapted to the individual clinical situation—frequent electrolyte determinations if diabetes insipidus has been diagnosed, lactate monitoring in acidotic donors, and repeated coagulation profiles in the presence of disseminated intravascular coagulation.

If infection is suspected, blood, urine, sputum, cerebrospinal fluid, and wound drainage cultures must be obtained. Routine surveillance cultures (usually blood and urine cultures) may be required, depending on the protocol of the local OPO and the organ type. Blood cultures should be obtained using peripheral venipuncture, rather than arterial or central venous catheters, to avoid contamination. Prophylactic antibiotics only should be administered immediately before the retrieval procedure. Any source of infection should be identified, characterized from a microbiologic standpoint, and treated.

General Management Goals

The most important overall goal in the management of brain-dead multiple-organ donors is to optimize organ perfusion and tissue oxygen delivery. Organ viability and function after transplantation are closely correlated with adequacy of resuscitation

TABLE 185.8

MANAGEMENT OF THE DECEASED ORGAN DONOR: SELECTED EVIDENCE PUBLISHED 1993–2009[a]

Study design	Study	Outcome	No. of cases	Level of evidence	Reference
Effect of standardized medical and institutional donor management protocols and pathways					
Individual case control study	Effect of critical donor pathway (including hormonal resuscitation protocol component)	Significant increase of organs procured, organ quality unchanged	270	3b	[15]
Case series	Aggressive hemodynamic monitoring, intervention, and hormonal resuscitation in marginal donors	High organ recovery rates from marginal donors	52	4	[17]
Individual case control study	Impact of hospital-based OPO coordinators on conversion rates	Higher donor conversion rate in hospitals with hospital-based OPO coordinators	NA	4	[75]
Retrospective cohort study	Effect on intensive lung donor management protocol on organ yield	Increased lung yield in the intensive early donor management group	182	4	[23]
Effect of donor pretreatment—Single pharmacologic agents					
Retrospective cohort study	Effect of catecholamine administration to brain-dead donors on graft survival	Catecholamine use associated in dose-dependent manner with significantly better kidney graft survival	3,890	4	[108]
Retrospective cohort study	Effect of dopamine administration on quality of early graft function in the recipients	Lower recipient delayed graft function rates and faster creatinine decrease in the dopamine group	254	4	[107]
RCT	Effect of continuous low-dose dopamine infusion in stable donors with normal renal function on early recipient graft outcomes	Decreased posttransplant need for > 1 dialysis session; no effect on rejection and short-term graft survival	265	2b	[109]
Individual case control study	High-dose steroids and aggressive management for marginal lung donors	No graft survival differences for lungs from marginal vs. standard donors	194	3b	[154]
RCT	Effect of high-dose continuous steroid infusion in liver donors on posttransplant outcomes	Improved posttransplant clinical reperfusion parameters (liver enzymes, bilirubin) and less early liver rejection for grafts from the steroid group	100	2b	[153]
RCT	Effect of intensive lung donor management protocol + (steroids or T3 or [steroids + T3] or placebo) on prerecovery lung quality and lung yield	No effect of pharmacologic pre-recovery interventions on lung yield; significantly less extravascular lung water accumulation in steroid groups	60	2b	[23]
Retrospective cohort study	Effect of donor desmopressin use on pancreas graft thrombosis rates (UNOS recipient database)	Higher thrombosis rates in pancreas grafts from donors that had received desmopressin	2,804	4	[91]
Retrospective cohort study	Effect of use of individual drugs on organ yield (UNOS donor database)	Favorable impact of steroids or desmopressin, but not T4, on organ yield	15,601	4	[123]
RCT	Effect of low-dose vasopressin vs. saline on donor hemodynamics and inotrope use	Increase in blood pressure and decrease in inotrope use in vasopressin group	24	2b	[110]
RCT	Effect of T3 infusion (limited to the duration of the organ procurement operation) vs. no T3	No differences for posttransplant liver graft function	25	2b	[124]
RCT	Effect of T3 infusion (within > 5 h of organ recovery) vs. none on donor hemodynamics and adenine nucleotide concentration measured in graft biopsy tissue	No differences in hemodynamics and adenine nucleotide levels	52	2b	[145]
Effect of donor pretreatment—Combination hormonal replacement therapy					
Retrospective cohort study	Requirements for adrenergic support of donors receiving thyroxin + steroids + insulin vs. steroids only vs. no hormonal therapy	Less adrenergic support required in donors receiving thyroxin + insulin + steroids	119	4	[127]
Individual case control study	Effect of T3 + steroids + insulin on need for inotropic support and organ yield in unstable donors	Hormonal treatment improved hemodynamics of unstable donors and resulted in similar organ yield as in stable donors	47	4	[127]

(*continued*)

TABLE 185.8

CONTINUED

Study design	Study	Outcome	No. of cases	Level of evidence	Reference
Retrospective cohort study	Impact on organ yield of (T3 or thyroxin) + steroids + vasopressin vs. none	Increased kidney, liver, pancreas, heart, and lung yield rates in donors that received hormonal replacement therapy	10,292	4	[20]
Retrospective cohort study	Impact of (T3 or thyroxin) + steroids + vasopressin vs. all other (> 3 hormones) hormonal replacement regimens on heart yield and early heart graft function	Increased number of transplanted hearts and improved early heart graft function	4,543	4	[19]
RCT	Effect of intensive lung donor management protocol and (steroids or T3 or [steroids + T3] or placebo) on lung quality and yield	No effect of steroids + T3 on donor lung quality and yield	60	2b	[23]
Retrospective cohort study	Effect of steroids + T4 on organ yield (UNOS donor database)	No effect of steroids + T4 on organ yield	15,601	4	[123]

[a]Levels of evidence (range: 1A [highest]—5[lowest]) were assigned based on current guidelines published by the Oxford Centre for Evidence Based Medicine (www.cebm.net).
NA, not applicable; OPO, organ procurement organization; RCT, randomized controlled clinical trial; T3, triiodothyronine; T4, thyroxin; UNOS, United Network for Organ Sharing.

and hemodynamic stability during the organ donor maintenance phase.

The events associated with the cause of brain death (e.g., hemorrhagic shock, cardiac arrest) can lead to significant physiologic abnormalities. Head injury preceding brain death is known to induce a hypermetabolic response, equivalent to that observed after a second- or third-degree burn involving approximately 40% of the total body surface area. Significant metabolic stress and impairment of organ perfusion occur during brain herniation, and both events are related to excessive catecholamine release. Any additional circulatory compromise in the time period afterward potentiates the deleterious consequences of these previous adverse events. Posttransplant organ function can be negatively affected by such episodes of cardiovascular dysregulation, particularly in such ischemia-sensitive organs as the heart and liver. For example, even with optimal heart donor management the recipient often needs inotropic support and may exhibit subendocardial myocyte necrosis on biopsy specimens obtained during the early posttransplant period [18,102]. Anticipating these changes associated with brain death and providing optimal management should they occur during the organ donor maintenance phase, as well as optimizing organ function, are of utmost importance [18].

Parameters associated with adequate tissue perfusion in stable donors in the absence of lactic acidosis are listed in Table 185.7. They include systolic blood pressure of 100 to 120 mm Hg, central venous pressure of 8 to 10 mm Hg, oxygen saturation of the arterial blood greater than or equal to 95%, core temperature greater than or equal to 35°C, and hematocrit of 30% to 35% [15,25], the latter balancing the slightly decreased oxygen transport capacity of the red blood cell mass with the beneficial effects of low viscosity on blood flow. Maintaining adequate hemoglobin concentration is also essential in preparation for organ recovery, in which hemodynamic stability throughout the operation is crucial, especially if blood loss occurs.

The use of vasopressors should be minimized if at all possible because of their splanchnic vasoconstrictive effects. Efforts to elevate blood pressure beyond the normal range can adversely affect outcome and should be avoided: High doses of vasopressors can cause arrhythmias and increase myocardial oxygen consumption, and pulmonary edema after excessive fluid administration can render lungs unsuitable for transplantation. After the lung, the pancreas is the organ most prone to tissue edema. Normal central venous pressure and low positive end-expiratory pressure (PEEP) help maintain an adequate perfusion gradient across the hepatic microcirculatory bed (i.e., that between the portal vein and hepatic artery on one side and the inferior vena cava and right atrium on the other).

Selective use of pulmonary artery catheterization must be considered in donors who do not respond to routine management and continue to exhibit hypotension or persistent lactic acidosis after adequate volume loading, particularly in those in whom this occurs despite use of moderate doses of dopamine. Determining pulmonary artery and capillary wedge pressures, cardiac output and index, pulmonary and systemic vascular resistive indices, oxygen availability and consumption, and other parameters helps to differentiate the cause of instability. Appropriate therapy can then be administered (e.g., fluid balance correction or PEEP adjustments, additional inotropic support, preload or afterload reduction). Once the hemodynamic instability has resolved, pulmonary artery catheters should be removed promptly to eliminate the inherent risks of infection, induction of arrhythmias, and mechanical endomyocardial damage.

A potential management conflict exists when the lungs are to be procured in combination with other organs from the same donor. Maintaining a central venous pressure of 8 to 10 mm Hg usually represents an acceptable compromise between the need for sufficient hydration to maintain adequate perfusion and good diuresis versus the dangers of provoking pulmonary edema in potential lung donors. Overall, optimizing hemodynamic parameters is paramount during the donor maintenance phase. Hypotension must be treated aggressively by proper fluid management, while minimizing the use of vasopressors. Hypertensive crises and tachyarrhythmic episodes require prompt intervention. PEEP that exceeds 5 cm H_2O should be used with caution, because hypotension may ensue.

Cardiovascular Support

Hypotension is the most common hemodynamic abnormality seen in brain-dead organ donors. The usual cause is hypovolemia, due to a combination of vasomotor collapse after brain death and the effects of treatment protocols to decrease intracranial pressure, which require minimizing hydration and use of osmotic diuretics (Tables 185.9 and 185.10). After brain death is declared, adequate volume resuscitation of the donor can require several liters of fluid. Until a euvolemic state is achieved, dopamine (greater than 3 µg per kg per minute) can be used temporarily; the dose should be titrated to maintain an adequate systolic blood pressure [15,25]. Infusion rates greater than 10 µg per kg per minute have been associated with increased rates of acute tubular necrosis and decreased renal allograft survival. High infusion rates also lead to decreased perfusion of other organs due to splanchnic vasoconstriction.

Dopamine is also the drug of choice if hemodynamic instability persists after fluid resuscitation and adequate volume loading. Use of isoproterenol and dobutamine should be avoided in this context because of their vasodilatory effects. Drugs with α-adrenergic agonist effects such as phenylephrine (IV infusion 0.15 to 0.75 µg per kg per minute) should be added only if hypotension persists in the face of euvolemia and titration of the dopamine infusion up to 15 µg per kg per minute. α-adrenergic agonists can cause severe peripheral vasoconstriction and reduce renal and hepatic perfusion; for this reason they must be used judiciously. Once these drugs are used, the need for their continued use must be frequently reassessed. Similar considerations apply to the use of epinephrine and norepinephrine (IV infusion up to 0.05 µg per kg per minute) [25]. For the majority (> 80%) of donors, adequate hemodynamic goals can be achieved with volume resuscitation and low-to-moderate doses of a single vasopressor agent (dopamine). Interestingly, recent studies have suggested a beneficial impact on early graft function and on graft survival of administration of catecholamines, and in particular of dopamine, to brain-dead patients [107–109]. Several potential mechanisms have been invoked to explain these observations, including a favorable modulatory effect on ischemia-reperfusion and on the upregulation of adhesion molecules that results from the inflammatory state induced by brain death [107–109]. Low-dose arginine vasopressin can serve as an additional or alternative vasopressor. It enhances vascular sensitivity to catecholamines, and may thus allow minimizing their dose and side effects [110–112]. Effective arginine vasopressin doses for improving hemodynamic stability range from 0.01 to 0.1 units per minutes, given as continuous intravenous infusion [111,112].

Measurement of urine output alone as a means of assessing adequacy of fluid resuscitation is notoriously unreliable in brain-dead donors. The presence of a systolic blood pressure between 100 and 120 mm Hg, a central venous pressure between 8 and 10 mm Hg, and the absence of metabolic acidosis (with or without infusion of a small amount of dopamine) with concurrent adequate urine output (at least 1 to 2 mL per kg per hour) are usually better indirect indicators of donor stability and sufficient oxygen delivery to organs and tissues. It is important to remember, however, that the use of vasoconstrictor or inotropic agents does not serve to replace adequate fluid resuscitation. Thus, proper fluid management remains the cornerstone of successful donor management.

When attempting to determine the etiology of hypotension in an organ donor, underlying cardiac disease (e.g., coronary artery disease, valve defects) and factors related to the cause of brain death (e.g., myocardial infarction, cardiac tamponade, or myocardial contusion) must be included in the differential diagnosis. Electrolyte abnormalities such as hypophosphatemia, hypocalcemia, hypokalemia, and hypomagnesemia are common in brain-dead organ donors. The presence of these entities must also be considered when hemodynamic instability is encountered, and frequent testing and correction of these significant electrolyte imbalances are important. Hypophosphatemia and hypocalcemia can decrease myocardial contractility and provoke hypotension [113]; hypokalemia and hypomagnesemia can impair hemodynamics by causing arrhythmias.

As a general rule, medications that possess rapid reversibility and a short half-life should be chosen to treat arrhythmias or hypertension. Hemodynamic instability can be pronounced after brain death, with wide swings between the extremes of hypotension and hypertension, rendering the brain-dead donor more susceptible to cardiovascular drug effects. Hypertension

TABLE 185.9

DIFFERENTIAL DIAGNOSIS OF HYPOTENSION IN THE BRAIN-DEAD ORGAN DONOR

Diagnosis	Common underlying cause(s)
Hypovolemia	See Table 185.10
Hypothermia	Loss of central temperature control, administration of room-temperature intravenous fluids and blood products, heat loss during laparotomies and thoracotomies
Cardiac dysfunction	Arrhythmia (ischemia, catecholamines, hypokalemia, hypomagnesemia) Acidosis Hypo-oxygenation Excessive positive end-expiratory ventilatory pressure Congestive heart failure due to excessive fluid administration Hypophosphatemia Causes related to the injury leading to brain death (cardiac tamponade, myocardial contusion) Myocardial sequelae of autonomic storm Preexisting cardiac disease
Drug side effect or overdose	Long-acting beta-blocker, calcium channel antagonist, antihypertensive agent
Hypocalcemia	Transfusions, hypomagnesemia (e.g., secondary to osmotic diuresis), acute renal failure

TABLE 185.10

DIFFERENTIAL DIAGNOSIS OF HYPOVOLEMIA IN THE BRAIN-DEAD ORGAN DONOR

Arterial and venous vasomotor collapse due to loss of central neurohumoral control
Dehydration (fluid restriction to treat head injury)
Insufficient resuscitation after the injury leading to brain death (e.g., ongoing hemorrhagic shock with coagulopathy after polytrauma)
Polyuria
Osmotic diuresis (mannitol, hyperglycemia)
Diabetes insipidus
Hypothermia
Administration of other diuretics
Massive third spacing in response to the original injury
Decreased intravascular oncotic pressure after excessive resuscitation with crystalloid fluids

can be treated with short-acting vasodilatory agents (e.g., nitroprusside) or a rapidly reversible β-adrenergic antagonist (e.g., esmolol hydrochloride), because hypertension usually is associated with increased circulating catecholamines. Other drugs, such as calcium channel blockers (e.g., verapamil, nifedipine) or longer-acting beta-blockers (e.g., labetalol, propranolol), should be avoided because of their negative inotropic effects and the inability to titrate them precisely. Bradyarrhythmias during the early phase of brain herniation are part of Cushing's reflex and do not usually require any treatment, unless they are associated with hypotension and asystole. Because of the lack of chronotropic effects by atropine after brain death, use of either isoproterenol or epinephrine is required to treat hemodynamically significant bradyarrhythmias.

Tachyarrhythmias are associated with the increased catecholamine release that occurs during and immediately after brain herniation. Administration of short-acting beta-blockers (e.g., esmolol hydrochloride) serves not only to treat arrhythmias but also to mitigate hypertension during the autonomic storm. Use of additional short-acting IV antiarrhythmics (e.g., lidocaine) may become necessary if tachyarrhythmias do not resolve after beta-blocker therapy. Calcium channel blockers (e.g., verapamil) must be avoided under these circumstances because of their negative inotropic effects. Cardiac glycosides (e.g., digoxin) also should not be used because they can induce and potentiate bradyarrhythmias and tachyarrhythmias, and they also have splanchnic vasoconstrictive side effects.

Cardiac arrest occurs in up to 25% of all donors during the maintenance phase after brain death and should be treated by routine measures, with the exception that isoproterenol or epinephrine must be substituted for atropine [84,86]. No intracardiac injections should be given during cardiopulmonary resuscitation because they can render the heart unsuitable for transplantation.

Respiratory and Acid–Base Maintenance

Use of endotracheal suctioning should be minimized during the treatment of cerebral edema to avoid any unnecessary stimulation that would increase intracranial pressure. In contrast, after brain death is declared, vigorous tracheobronchial toilet is important, with frequent suctioning using sterile precautions. Percussion and turning for postural drainage are instituted as well. Even if the lungs are unsuitable for donation, it is important to minimize the risk of atelectasis and infection. Preventing atelectasis facilitates oxygenation and may obviate the need for detrimental high levels of PEEP. Steroids administered to some patients as part of the treatment for increased intracranial pressure predispose to pulmonary infectious complications. The presence of pneumonia can preclude donation of the lungs as well as other organs, depending on its severity and association with systemic sepsis. Routine respiratory care of all donors also includes the use of 5 cm H_2O PEEP to increase alveolar recruitment and prevent microatelectasis [15,25].

In potential lung donors the endotracheal tube should not be advanced more than several centimeters into the trachea, to prevent damage to areas that may become part of an anastomosis. A sample of sputum should be obtained for Gram's stain and cultures to exclude the presence of infection. The samples can be obtained using bronchoscopy, a procedure that is often routinely performed before lung donation. Peak end inspiratory airway pressures should be less than 30 cm H_2O. Traditionally, tidal volumes of 10 to 12 mL per kg have been recommended. However, it is not clear at present to what extent the evidence supporting lung protective strategies for many regular ICU patients—that is, tidal volumes of 6 to 8 mL per kg—also applies to the management of the often injured lungs of brain-dead donors as well [25,114,115]. For now, though, it appears prudent to apply pulmonary management principles that have proven beneficial for general ICU patients also to potential organ donors. For potential lung donors, the lowest FIO_2 that is capable of maintaining a PaO_2 of greater than 100 mm Hg should be selected. If oxygenation is insufficient, PEEP should be increased rather than increasing the FIO_2. High levels of PEEP negatively affect cardiac output, which should be carefully monitored in this setting. If hypotension occurs, PEEP should be reduced. Under these circumstances, use of pulmonary artery catheterization generally should be considered to balance PEEP requirements against those of organ perfusion. In contrast, to correct insufficient arterial oxygenation in non–lung donors, an increase in FIO_2 is preferred over high levels of PEEP [25].

The etiology of pulmonary edema in organ donors can be cardiogenic, neurogenic, aspiration induced, a result of trauma or fluid overload, or a combination of these factors. Neurogenic pulmonary edema usually precludes lung or combined heart–lung donation, but not donation of other organs (e.g., heart, kidney, liver, and pancreas). The treatment for pulmonary edema is supportive and should be directed at maintaining adequate arterial oxygenation without using high levels of PEEP. Fluids must be administered carefully to maintain organ perfusion while avoiding exacerbation of the edema. Excessive use of crystalloid fluids during the initial resuscitation after brain death is declared can render the lungs unsuitable for transplantation. If large amounts of fluid are required, colloids (e.g., albumin solutions) or blood transfusions (if the hemoglobin is less than 8 g per dL) should be considered in addition to the infusion of crystalloid solutions [15].

Respiratory alkalosis can develop in brain-dead organ donors secondary to mechanical hyperventilation as part of the treatment protocol for elevated intracranial pressure. After brain death, the arterial pH should be adjusted to normal values because alkalosis has many undesirable side effects, such as increased cardiac output, systemic vasoconstriction, bronchospasm, and a shift to the left of the oxyhemoglobin dissociation curve [15]. The latter decreases oxygen unloading in the tissues and impairs oxygen delivery, thereby diminishing tissue oxygenation and metabolism. Lactic metabolic acidosis is frequent in brain-dead donors; it should be treated by compensation with a slight respiratory alkalosis until the underlying abnormality has been corrected (e.g., dehydration, tissue ischemia). Administration of sodium bicarbonate should be contemplated only if the increased minute ventilation necessary to induce respiratory alkalosis leads to a decrease in cardiac output. In either situation, the most important aspect of managing metabolic acidosis is to treat the underlying cause. In rare cases, this may require pulmonary artery catheterization to assess the adequacy of hydration, cardiac output, and tissue oxygen delivery.

Renal Function and Fluid and Electrolyte Management

Maintaining adequate systemic perfusion pressure and brisk urine output (greater than 1 to 2 mL per kg per hour), while minimizing the use of vasopressors, contributes to good renal allograft function and reduces the rate of acute tubular necrosis after transplantation. If the urine production is still insufficient (e.g., less than 0.5 mL per kg per hour) after adequate volume loading, loop diuretics (furosemide, ethacrynic acid, bumetanide) or osmotic diuretics (mannitol) can be considered to initiate diuresis. Nephrotoxic drugs (e.g., aminoglycosides) and agents that may exert adverse effects on renal perfusion (e.g., nonsteroidal anti-inflammatory drugs) are contraindicated. Cephalosporins, monobactams, carbapenems,

and quinolones are examples of less nephrotoxic but effective antibiotics that can be used if infection occurs.

Polyuria in brain-dead donors is a frequent finding. It can be due to diabetes insipidus, osmotic diuresis (induced by mannitol administered to decrease elevated intracranial pressures or hyperglycemia), physiologic diuresis due to previous massive fluid administration during resuscitation after the original injury with return of third-space fluid into the intravascular space, or hypothermia. Diabetes insipidus often heralds brain death in head-injured patients. It is the most frequent cause of polyuria during the organ donor maintenance phase. Found in up to 80% of all brain-dead bodies [82], it is related to insufficient blood levels of antidiuretic hormone (vasopressin), resulting in the production of large quantities of dilute urine. Diabetes insipidus should be suspected when urine volumes exceed 300 mL per hour (or 7 mL per kg per hour) in conjunction with hypernatremia (serum sodium greater than 150 mEq per dL), elevated serum osmolality (greater than 310 mOsm per L), and a low urinary sodium concentration. In addition to hypernatremia, other electrolyte abnormalities frequently observed during diabetes insipidus include hypokalemia, hypocalcemia, and hypomagnesemia. The appropriate replacement of these electrolyte losses can be guided by urinary electrolyte determinations, which easily allow calculation of the amount of the electrolyte to be replaced. Because diabetes insipidus is so common, mannitol administration should be discontinued after brain death is declared. Other supportive care of patients with diabetes insipidus includes replacing urine output milliliter for milliliter with free water (e.g., 5% solution of dextrose in water IV). Once urine output due to diabetes insipidus exceeds 300 mL per hour, desmopressin (desamino-8-d-arginine vasopressin), a synthetic analog of vasopressin, or arginine vasopressin, should be administered. Desmopressin has a long duration of action (6 to 20 hours) and a high antidiuretic–pressor ratio, avoiding any undesirable splanchnic vasoconstrictive effects that can occur with administration of normal- and high-dose arginine vasopressin [25,110,116]. For example, doses of 1 to 2 µg desmopressin are administered intravenously every 8 to 12 hours to achieve a urine output less than 300 mL per hour [116]. Desmopressin can also be effectively administered subcutaneously, intramuscularly, and intranasally. Vasopressin IV infusion can be started at 0.5 units per hour and titrated up to 6 units per hour, targeting a urine output of 0.5 to 3 mL per kg per hour and a serum sodium of 135 to 145 mEq per L [25,110]. Compared to desmopressin, arginine vasopressin is easier titrated and adds beneficial hemodynamic effects.

During the initial resuscitation phase after brain death is declared, infusion solutions with low sodium content should be used. Subsequently, maintenance fluid should consist of 5% dextrose in 0.45% sodium chloride with 20 mEq potassium added to each liter, administered at a rate of 2 mL per kg per hour during the maintenance phase if urine output is adequate (greater than 1 to 2 mL per kg per hour). If the urine output is greater than 2 mL per kg per hour, IV fluids should be administered at a rate equal to the urine output during the previous hour (IV intake = urine output). If the serum sodium concentration exceeds 150 mEq per dL, the maintenance fluid should consist of 5% dextrose solution with 20 mEq potassium added to each liter. Should the hourly fluid administration rate exceed 500 mL per hour, the dextrose concentration of the maintenance fluid should be decreased to 1% to avoid excessive hyperglycemia. IV maintenance fluids administered to brain-dead organ donors must always contain glucose, which is important to maintain intrahepatic glycogen stores that appear to be associated with normal liver allograft function in the early posttransplant period. The sodium content of certain IV fluids and plasma expanders (e.g., albumin solutions) also must be taken into consideration in hypernatremic patients.

The use of blood transfusions and other blood products should be minimized in organ donors, as in other patients. If transfusion or blood component therapy is necessary, CMV-seronegative blood products or leukocyte filters, or both, should be used whenever possible [15]. All blood must be screened for HIV, HBV, and HCV, and seropositive units should not be used.

Endocrine Therapy

According to previous studies, pituitary hormone blood levels do not uniformly decrease after brain death. Diabetes insipidus develops in approximately 80% of brain-dead donors as a result of low or absent blood levels of vasopressin [82]. These findings are a direct consequence of brain death, which abolishes vasopressin production in the hypothalamic nuclei (supraoptic and paraventricular nuclei) and vasopressin storage and release in the posterior pituitary. In contrast, near normal levels of anterior pituitary hormones, such as thyroid-stimulating hormone, adrenocorticotropic hormone, and growth hormone, have been documented after brain death in some studies [117–120]. Their persistence is probably due to the preservation of small subcapsular areas in the anterior pituitary, the blood supply of which is derived from small branches of the inferior hypophyseal artery. The latter arises from the extradural internal carotid artery, which is relatively protected from increases in intracranial pressure [121]. Recent clinical evidence, however, suggests deficient adrenal cortisol secretion after dynamic stimulation in brain-dead donors, irrespective of the level of pituitary dysfunction [122].

The principle of pharmacologic replacement therapy for deficient posterior pituitary vasopressin after brain death is well established [15,25,110,111,116]. A UNOS database analysis demonstrated a significant association between desmopressin use in donors and organ yield (Table 185.8) [123]. Low-dose vasopressin has been shown to exert beneficial hemodynamic effect in brain-dead donors (Table 185.8) [110,111]. In contrast, controversy still exists regarding the benefits of supplementation with hormones synthesized by organs under anterior pituitary control (i.e., triiodothyronine [T3], thyroxine [T4], and corticosteroids) (Table 185.8) [15,19,20,21,25,123–133]. Initially, the presence of low T3 blood levels was demonstrated after brain death in animal experiments [134]. Administration of exogenous T3 to donor animals improved a variety of metabolic parameters before and after organ preservation [135–137], as well as organ function after transplantation [138]. These findings suggested possibly positive effects of T3 also in human donors. A limited number of uncontrolled clinical trials suggested favorable influences of donor pretreatment with thyroid hormone on hemodynamic and metabolic parameters during the donor maintenance phase [86,139,140] and on outcome after heart transplantation [141–143]. But a number of other investigators failed to observe a significant benefit of thyroid hormone administration on biochemical and hemodynamic donor parameters and on posttransplant outcomes (Table 185.8) [23,123,124,132,144–146].

The latter outcomes could be explained at least in part by the findings of some studies which have suggested that the low T3 levels in human donors do not correlate with the presence of hemodynamic stability [147,148] or outcome after transplantation [149–152] to begin with. The typical thyroidal hormonal pattern after brain death consists of decreased T3, normal or decreased thyroxine, and normal thyroid-stimulating hormone. This pattern is not consistent with acute insufficiency of the hypothalamic–pituitary–thyroid axis or clinically overt hypothyroidism, but is similar to changes observed in other groups of critically ill individuals [130]. Thyroid hormone administration to such patients may not only be ineffective but

may theoretically even be detrimental in some cases [130,131]. In summary, there is no conclusive evidence to date that supplementation of organ donors with thyroid hormone *alone* yields a significant clinical benefit.

By contrast, evidence for the potential benefits of routine administration of corticosteroids *alone* is emerging [23,123,153,154]. Normal human serum adrenocorticotropic hormone and cortisol levels have been demonstrated after brain death in some studies [117–120], while others have observed dysfunction of the hypothalamic–pituitary–adrenal axis in patients with traumatic brain injury [119]. Clinically, however, administration of high-dose steroids was noted to stabilize and improve lung function, leading to higher probability of lung recovery from brain-dead patients that had previously not been considered for lung donation, to increase organ yield and to lead to improved outcomes after liver transplantation [15,123,153–156].

Published retrospective evidence suggests that institution of empiric donor management protocols that incorporate *combination* treatment with arginine vasopressin, high-dose corticosteroids, thyroid hormone, and insulin may stabilize and improve cardiac function in brain-dead donors and may result in increased probability of kidney, heart, liver, lung, and pancreas recovery and transplantation and may improve posttransplant outcomes (Table 185.8) [17,19–20,126–129]. These and other findings have served as the basis for recommendations from a national U.S. consensus conference held in 2001 that include: T3: 4 µg bolus, 3 µg per hour continuous infusion; arginine vasopressin: 1 unit bolus, 0.5 to 4.0 units per hour continuous infusion (titrate SVR to 800 to 1,200 using a PA catheter); methylprednisolone 15 mg per kg intravenous bolus, repeat every 24 hours; and insulin continuous intravenous infusion at a minimum rate of 1 unit per hour (titrate blood glucose to 120 to 180 mg per dL) [16,18]. However, given the uncertainty regarding potentially adverse side effects and the absence of high-level evidence, large prospective randomized trials are necessary before routine administration of hormonal combination therapy can be recommended for all donors—particularly because, for example, excellent lung procurement rates from marginal donors and good posttransplant outcomes have also been described in the current era without hormonal supplementation (Table 185.8) [157]. Moreover, the optimal dose and combination, and the contribution of each individual hormone to the observed overall outcome remain yet to be studied and elucidated. The above-mentioned findings have stimulated national prospective multicenter trials that investigate the optimal timing and outcome of combination hormone replacement therapy. Although these trials are ongoing, it appears prudent to reserve routine *combination* hormone replacement therapy for hemodynamically unstable donors that require substantial catecholamine doses (e.g., dopamine > 10 µg per kg per min) or have an ejection fraction of less than 45% [16,18,25].

Although brain death is not associated with primary pancreatic endocrine dysfunction, hyperglycemia is frequent in brain-dead donors. Hyperglycemia can be caused by increased catecholamine release, altered carbohydrate metabolism, steroid administration for treatment of cerebral edema, infusion of large amounts of dextrose-containing IV fluids, or peripheral insulin resistance. Treating hyperglycemia in brain-dead donors appears to be important with regard to pancreatic islet cell function. Experimental evidence suggests that high glucose levels may produce transient or irreversible damage to beta cells in the pancreatic islets, in vitro and in vivo [158,159]. This glucose toxicity was attenuated during in vivo experiments by correcting hyperglycemia [160]. Clinical studies in pancreas transplant recipients have demonstrated that donor hyperglycemia is a risk factor for decreased graft survival [90]. It was not established in these studies, however, whether donor hyperglycemia was indicative of marginal or insufficient beta-cell mass or whether impaired pancreatic graft function was related to islet cell dysfunction as a result of hyperglycemia.

Hyperglycemia in and of itself is known to cause insulin resistance [161]. Studies in brain-dead donors have suggested that a state of hyperinsulinemia coupled with peripheral insulin resistance exists, as evidenced by elevated C-peptide–glucose molar ratios [162]. For all the above reasons, it is prudent to maintain blood glucose levels in donors between 120 and 180 mg per dL [163]. Insulin should be administered as needed according to the blood glucose values to mitigate any potential adverse effects of hyperglycemia on pancreatic islets, which could impair glucose homeostasis after transplantation [163]. If hyperglycemia persists despite initial bolus insulin therapy, continuous IV insulin infusion should be instituted to facilitate titration of glucose levels. As in many other critical care patients, good glycemic control is also good standard practice for brain-dead donors, since it acts to prevent ketoacidosis and osmotic diuresis, both of which can be significant problems in the management of brain-dead donors, and since it may contribute to improved overall organ recovery and transplantation rates [164].

Hypothermia

After brain death, the body becomes poikilothermic because of the loss of thalamic and hypothalamic central temperature control mechanisms, and hypothermia usually ensues [165]. Systemic vasodilation causes additional heat loss. Hypothermia can be aggravated by administering room-temperature IV fluids and cold blood products. Adverse effects of hypothermia include decreased myocardial contractility, hypotension, cardiac arrhythmias, cardiac arrest, hepatic and renal dysfunction, and acidosis and coagulopathy [166–168]. Therefore, donor core temperature must be maintained at or above 35°C. It is usually sufficient to use humidified, heated ventilator gases; warmed IV fluids and blood products; and warming blankets to achieve rewarming and to maintain an adequate body temperature. Rewarming with peritoneal dialysis or bladder irrigations generally should not be performed in organ donors.

Coagulation System

Coagulopathy and disseminated intravascular coagulation are common findings in brain-dead donors, particularly after head injuries. Pathologic activation of the coagulation cascade occurs when brain tissue, which is very rich in tissue thromboplastin, comes in contact with blood after trauma. Massive blood transfusions can produce dilutional thrombocytopenia, and subsequent ongoing hemorrhage, hypothermia, and acidosis are all able to trigger or further aggravate coagulopathy. Clinical findings can include pathologic bleeding, abnormal prothrombin time, thrombocytopenia, hypofibrinogenemia, and increased levels of fibrin/fibrinogen degradation products. Treatment of coagulopathy entails use of blood components such as platelets, fresh-frozen plasma, or cryoprecipitate and correction of the underlying pathophysiology (e.g., hypothermia, acidosis, surgical hemorrhage). ε-Aminocaproic acid should not be used because of its potential for inducing microvascular thrombosis, thereby rendering organs potentially unsuitable for transplantation.

Other Aspects

Brain death may also adversely affect the donor's nutritional status. Experimental studies have suggested a hypercatabolic state and decreased hepatic intracellular ATP levels [169].

Moreover, a suboptimal organ energy and redox status along with the inflammatory changes that result from the chemokine and cytokine release associated with brain death may exert a deleterious influence on the magnitude of, and recovery from, ischemia-reperfusion injury and on posttransplant organ function in the recipient. Appropriate nutritional support of the donor may be able to prevent depletion of micro- and macronutrients and may attenuate oxidative stress and ischemia-reperfusion injury. However, currently there is no clinical data available that would directly support routine nutritional supplementation of brain-dead donors [169].

Various pharmacologic donor pretreatment protocols to optimize donor and transplant outcomes have been reported. The clinically beneficial effects of administration of catecholamines, vasopressin (or its analogue desmopressin), and of steroids on both donor and posttransplant outcomes have already been discussed in detail above (Table 185.8) [23,107–109,123,153,154]. In other studies, verapamil mitigated the adverse impact of elevated cytosolic calcium levels on renal allograft function [170] after donor hemodynamic instability. Finally, donor pretreatment with immunosuppressants may have a favorable impact by preventing upregulation of proinflammatory pathways and increased expression of major histocompatibility complex molecules that have been demonstrated to occur after brain death [102,103,104]. The latter pretreatment modalities, however, must be investigated more extensively before they can be routinely applied.

Multiple-Organ Donor Operation

After consent is obtained, the OPO schedules and organizes the organ recovery operation. Often, several surgical teams from different locations participate; their transportation and the preparation of the recipients in the various hospitals must be meticulously coordinated. After certification of death according to the state laws occurs, the brain-dead donor is brought to the operating room. Full cardiovascular and ventilatory support is maintained throughout the operation, until the organs are flushed and cooled. The principles of brain-dead donor management should be reviewed with the anesthesiologist, unless he or she is familiar with the specific clinical aspects of cardiovascular and ventilatory support for brain-dead organ donors. Hemodynamic stability must be maintained during the surgical organ retrieval, which is the equivalent of a combined major abdominal and thoracic operation and can last up to several hours. Transient tachycardia and hypertension may occur while the surgical incision is being made; they most likely reflect spinal reflexes causing vasoconstrictive responses and adrenal stimulation. Subsequently, consideration must be given to the increased heat loss caused by the wide abdominal and thoracic incisions and the duration of the surgery. Vecuronium or pancuronium should be used to inhibit reflex muscular contractions [83]. Tubocurarine should not be used in brain-dead donors because of its association with hypotension as a consequence of histamine release and ganglionic blockade. Maintenance fluid administration throughout the operation must take into account the significant intraoperative fluid losses resulting from extensive dissection with evaporation and blood loss, transsection of lymphatic channels, and massive third-space fluid loss.

All organs to be recovered are completely mobilized, and their vascular pedicles are dissected free. At the end of the operation, systemic heparinization occurs and cannulas are inserted (depending on the organs to be procured) into the abdominal aorta, inferior vena cava, portal vein, aortic arch, and pulmonary artery. Only then is circulatory and respiratory support terminated. The organs are flushed in situ with preservation solution to remove blood and to cool the organs to a temperature of 4°C to 7°C. Simultaneously, topical external cooling is provided by the application of sterile ice slush. The organs are then individually removed, by dividing the remaining attachments and vascular pedicles, and then packaged [49]. Storage in preservation solution at 4°C to 7°C in a cooler surrounded by crushed ice allows maximal preservation times of 4 to 6 hours for heart and lungs, approximately 30 hours for livers and pancreata, and about 40 hours for kidneys. These preservation constraints are taken into consideration as organs are allocated. Critical care of the donor ends when controlled cardiac arrest occurs at the completion of the surgical organ recovery. This finality is ephemeral, however, because it results in the start of new lives for the recipients after a successful organ transplant.

PERIOPERATIVE CRITICAL CARE MANAGEMENT OF THE DONATION AFTER CARDIAC DEATH ORGAN DONOR

Preoperative Care of the Potential DCD Donor (Prior to Obtaining Consent for Organ Donation)

Therapy in those patients must remain primarily aimed at treating the underlying pathology (e.g., head trauma, cerebrovascular accident). Any premature (i.e., prior to the family having made the decision to withdraw care and prior to obtaining consent) change of therapeutic objectives would be unethical and may lead to lower consent rates, thereby further exacerbating the current donor organ shortage [26,28,98].

Preoperative Care of the Actual DCD Donor (After Having Obtained Consent for Organ Donation)

Once consent to proceed with organ donation has been obtained, the focus switches from cerebral protection to preservation of organ function and optimization of peripheral oxygen delivery [26,98]. Maintenance therapy endpoints in DCD donors are identical to those that apply for brain-dead organ donors (Table 185.7). Since DCD donors usually do not exhibit the same pathophysiologic characteristics as brain-dead donors, general management principles for DCD donors are more akin to those that apply to non-brain–dead patients in the ICU that are described elsewhere in this book. Organ-specific considerations (e.g., use of catecholamines) are the same as those described below for brain-dead donors.

Preterminal and Intraoperative Care of DCD Donors

Maintenance therapy as outlined above is continued until support is withdrawn and the patient is extubated (either in the ICU or in the operating room). Any additional premortem interventions (e.g., surgical: insertion of femoral cannulas in preparation of organ recovery; pharmacologic: administration of intravenous heparin, opioids, and phentolamine) must occur in strict accordance with local OPO/hospital DCD protocols and policies [26,98,171–174]. Death is then pronounced by a physician (usually the patient's intensive care physician) not belonging to the organ recovery and transplant team according

to criteria that are specified by the local OPO/hospital DCD protocol.

Next, after an additional 2-to-5-minute waiting time, surgical organ recovery begins [26,173,174]. For DCD donors, the use of a rapid procurement technique is mandatory in order to minimize warm ischemia time, particularly when highly ischemia-sensitive organs such as the liver, pancreas, or lungs are to be recovered as well [49].

Disposition of the patient, if death does not occur within a specified waiting time post withdrawal of support, is determined by the local protocol (e.g., return of patient to a nonintensive care hospital floor for comfort care only).

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CHAPTER 186 ■ DIAGNOSIS AND MANAGEMENT OF REJECTION, INFECTION, AND MALIGNANCY IN TRANSPLANT RECIPIENTS

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Allograft rejection in transplant recipients is the side effect of the complex and intricate mammalian immune system, which is intended to defend the host against pathogens. The history of solid-organ transplantation has demonstrated that graft survival depends on manipulating the immune system. However, any modification of the host's defense mechanism can bring unwanted consequences, such as infection and malignancy. Throughout the development of solid-organ transplantation during the 1960s, it became clear that suppressing the immune system of the prospective host would be required for sustained graft function. In the infancy of this field, acute rejection (AR) and graft loss were the rule rather than the exception.

Subsequently, however, successful antirejection treatment and, more important, the ability to markedly reduce the incidence of rejection through preventive strategies allowed solid-organ transplantation to develop beyond its status as a sparingly performed investigational therapy. Specifically, successful allogeneic renal transplantation was achieved using a combination of a high-dose corticosteroid and azathioprine [1]. Contemporaneous observations of those early transplant recipients demonstrated that nonselective immunosuppressive therapy prolonged graft (and patient) survival yet led to an increased susceptibility to infection, often with unusual, opportunistic pathogens [2]. Furthermore, immunosuppressed transplant recipients also had an increased susceptibility to malignancy [3].

In the nearly 50 years since the report of the initial 12 recipients treated for rejection of allogeneic renal grafts, solid-organ transplantation has flourished beyond the expectations of any but the most wildly optimistic pioneers in the field. Kidney, liver, heart, and lung transplants are now standard-of-care therapies for end-stage renal, hepatic, cardiac, and pulmonary disease, respectively. Pancreas and pancreatic islet-cell transplants restore the beta-cell function in patients with diabetes mellitus. Even the small bowel has been successfully transplanted as a treatment for patients with short gut syndrome. Such strides have been made possible by the accumulated advances in organ procurement, preservation, surgical techniques, tissue typing, immunosuppressive therapy, and the use of antibacterial, antifungal, and antiviral agents for both prophylaxis and treatment of posttransplant infection. Table 186.1 lists some of the major advances in the management of rejection, infection, and malignancy in transplant recipients.

Yet even with the expanded immunosuppressive armamentarium of the twenty-first century, it remains difficult to adequately suppress the host immune system (to allow acceptance and even tolerance of the graft) without oversuppressing immune function (and thereby leaving the host vulnerable to opportunistic infection and malignancy). This chapter reviews the complications (namely, graft rejection, infection, and malignancy) of solid-organ transplantation on either side of that delicate balance. Special attention is directed toward opportunistic infections and unusual malignancies that occur in the immunosuppressed patient population.

REJECTION

Unlike the nonspecific innate immune system seen in all living organisms, the adaptive immune system—a unique property of jawed vertebrates—is an evolutionarily more advanced, efficient, "specific," and versatile host defense mechanism against invasion of pathogens. However, a side effect of the ability of the host immune system to recognize and attack "nonself" tissues is rejection of grafted tissues posttransplant. That side effect was observed clinically for centuries before Medawar demonstrated that it was an intrinsic property of the host immune system in response to foreign tissue [4]. The exogenous modulation of the host immune system to allow sustained graft function has proceeded along with—and often preceded—our understanding of the physiologic mechanism of rejection and tolerance.

Integral to our understanding of rejection is its immunologic basis. The immunologic disparity among members of the same species of mammals that leads to lack of recognition of "self" tissue and to rejection of nonself tissue is based on the differences in cell surface molecules that are expressed. In humans, these major histocompatibility antigens were first identified in leukocytes, and hence are termed *human leukocyte antigens* (HLAs). HLAs are subdivided into two classes: class I (HLA-A, -B, and -C), expressed on the surface of all nucleated cells, and class II (HLA-DR, -DQ, and -DP), expressed on the surface of *antigen-presenting cells* (APCs). The recognition of nonself tissue occurs via two distinct immunologic pathways: *direct* and *indirect allorecognition*. Direct allorecognition consists of recipient T-helper cells recognizing donor HLA disparity expressed on the donor cell surface. Indirect allorecognition consists of recipient APCs (generally thought to be activated macrophages, dendritic cells, and B lymphocytes) phagocytosing donor cellular debris, including HLAs, which are then processed and re-presented on the APC surface to be recognized by recipient T- helper cells (CD4+ lymphocytes).

In either pathway, costimulation signals between CD4+ T-helper lymphocytes and CD8+ cytotoxic T lymphocytes trigger a cascade of immunologic events. Interleukin (IL)-2, a crucial and early signal in immune activation, is secreted by activated CD4+ T-helper lymphocytes, engendering increased T-cell responsiveness, clonal expansion of alloreactive T lymphocytes, and acquisition of the cytolytic phenotype by host T lymphocytes. Direct allorecognition leads to a more immediate and vigorous immune response against foreign tissue, but, in both pathways, additional helper T lymphocytes are recruited and secrete a wide array of cytokines (e.g., IL-1, interferon-γ, tumor necrosis factor-α), facilitating the further recruitment of

TABLE 186.1

MAJOR ADVANCES IN MANAGEMENT OF REJECTION, INFECTION, AND MALIGNANCY IN TRANSPLANT RECIPIENTS

Topic	Major advances	Reference
Graft rejection	Desensitization protocols for patients with DSA	[6,32,33]
	Flow cytometry, Luminex-based cross-match	[7,8]
	Induction therapy and biologics reduce rejections	[10–16]
Fungal infection	Caspofungin and voriconazole	[99–102,104]
Viral infection	PCR for CMV and EBV detection	[114,115]
	Preemptive CMV therapy	[120–124,194]
	Liver transplants for patients with HBV or HCV	[137–142]
	Improved outcomes for recipients with HIV	[144–147]
Malignancy	Chemotherapy and rituximab beneficial for PTLD	[170,179,195]
	HHV-8 and posttransplant Kaposi sarcoma	[185–187]
	Liver transplant for patients with HCC	[191–193]

DSA, donor-specific antibody; PCR, polymerase chain reaction; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PTLD, posttransplant lymphoproliferative disease; HHV, human herpes virus; HCC, hepatocellular carcinoma.

cytotoxic T lymphocytes, natural killer cells, and B lymphocytes. Then, B lymphocytes begin to secrete antibody directed against the allogeneic tissue in ever-increasing quantities. Infiltration of the graft by such effector cells, the binding of antibody, and the activation of complement lead to rejection in its various forms (vide infra), which, if unchecked, results in graft loss (Fig. 186.1). Donor-recipient mismatches between HLAs may produce an immune response by either the direct or indirect pathways; however, minor non-HLA mismatches typically produce an immune response by the indirect pathway only.

Clinically, rejection is classified according to the temporal relation of graft dysfunction to the transplant operation and the histologic features seen in rejected tissue. The three main types of rejection are *hyperacute (HAR)*, *acute (AR)*, and *chronic (CR)*. Each type is mediated by a different host immune mechanism. Consequently, each type poses different problems for clinicians and researchers.

Hyperacute Rejection

HAR occurs within a few minutes to a few hours after the reperfusion of the graft posttransplant. Preformed antibodies directed against antigens presented by the graft mediate activation of complement, activation of endothelial cells, and formation of microvascular thrombi, leading to graft thrombosis and loss [5]. The process is irreversible; currently, no treatment is available. Because HAR is mediated by circulating preformed antibodies normally directed against ABO system (comprising the four main blood types, i.e., A, B, AB, and O) antigens or against major HLA antigens, thorough screening of potential transplant recipients should prevent nearly all HAR.

The panel-reactive antibody (PRA) assay is a screening test that examines the ability of serum from potential transplant recipients to lyse lymphocytes from a panel of HLA-typed donors. A numerical value, expressed as a percentage, indicates the likelihood of a positive cross-match to the donor population. Therefore, patients lacking preformed antibodies to random donor lymphocytes are defined as having a PRA of 0% and have a very low probability of eliciting a positive lymphocyte cross-match to any donor. The finding of a higher PRA identifies patients at high risk for a positive cross-match and thus for HAR and for subsequent graft loss. Most often, such patients were previously sensitized by childbirth, blood transfusions, or a prior transplant.

Pretransplant, cross-match testing is performed to identify preformed antibodies against class I HLAs (T-lymphocyte cross-match testing) and class II HLAs (B-lymphocyte cross-match testing). A strong positive class I-HLA cross-match immediately pretransplant is ordinarily an absolute contraindication to renal and pancreas transplants. At most centers, heart and liver transplants are performed without a cross-match, unless the recipient is highly sensitized or has previously received a graft possessing major antigens in common with the current donor (i.e., donor-specific antibody [DSA]). A positive B-lymphocyte crossmatch indicates preformed antibodies directed against class II HLAs and is a relative, but not absolute, contraindication to a transplant. Recent studies confirmed the

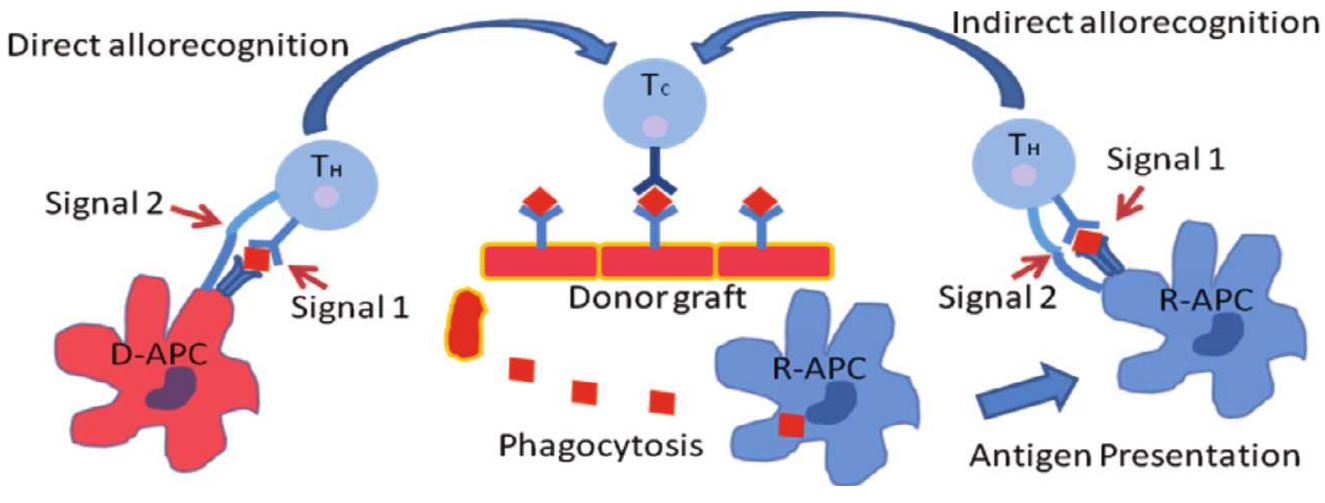

FIGURE 186.1. Direct, indirect pathways of allorecognition. Signal 1 is delivered through the T-cell receptor after engagement by a peptide–HLA complex. Signal 2, also known as costimulatory sign, is delivered by an array of cell-surface molecules on the T helper cell and the antigen-presenting cell (APC). D-APC, donor APC; R-APC, recipient APC; TH, T helper lymphocyte; Tc, cytotoxic T lymphocytes.

efficacy of plasmapheresis followed by administration of immune globulin to reduce PRA levels and to convert strongly positive crossmatch results to weakly positive or negative results, thereby allowing organs to be transplanted across what were previously considered as strong immunologic barriers [6].

Crossmatch testing is a vital tool to identify the presence of antibodies against potential donor antigens and to assess the risks of posttransplant rejection and subsequent graft loss. Ironically, cross-match testing methods are not standardized. Since the mid-1960s, cross-match testing was based on the complement-dependent cytotoxicity (CDC) assay. The CDC assay was further refined by adding a wash step and an antihuman globulin (AHG) step, to increase its sensitivity and specificity. Then, with the introduction of technology based on flow cytometry (FC), the presence of recipient antibody on the surface of donor lymphocytes could be detected independent of complement binding. The FC method further enhances the sensitivity of crossmatch and, since the late 1980s, has been adopted by an increasing number of transplant centers [7].

The latest development in anti-HLA antibody screening was the introduction of Luminex® technology, using HLA-coated fluorescent microbeads and FC. This method in theory pinpoints the DSAs in sera of recipients with high PRA levels. Since all transplant donors are HLA typed nowadays, a negative cross-match for recipients with high PRA levels can be ensured by avoiding the selection of donors carrying unacceptable antigens (virtual cross-match) [8].

The main concerns with these new developments in antibody typing and crossmatch testing are between-center test variability and the thresholds of defining false-negative results (results that could deny recipients with high PRA levels a chance for a potential lifesaving transplant). Currently, it is up to an individual transplant center to implement its own HLA typing and cross-match policy, depending on the center's experience and clinical outcomes.

Although screening has all but eliminated HAR as a clinical problem, active investigation is nonetheless directed at dissecting the underlying pathophysiologic mechanisms of HAR. Another research focus is on the similar rapid rejection of xenoreactive antigens that serve as a barrier to the development of xenotransplantation.

Acute Rejection

AR is the most common form of graft rejection in modern clinical transplantation. It may develop at any time, but is most frequent during the first several months posttransplant. Rarely, it occurs within the first several days posttransplant, a process termed *accelerated acute rejection* (AAR), most likely a combination of amnestic immune response driven by sensitized memory B lymphocytes and activation of the direct allorecognition pathway. Under such circumstances, the donor antigen exposure often occurred in the distant past, so the level of circulating DSAs would have been too low to be detected by conventional crossmatch techniques. Once challenged by the same donor antigens introduced by the organ transplant, dormant memory lymphocytes reactivate, replicate, and differentiate. Within several days, large numbers of antibodies are directed against the donor tissue and result in graft rejection.

Cellular rejection and antibody-mediated rejection (AMR) are not mutually exclusive in AR. Histologically, AR generates an infiltration of activated T lymphocytes into the graft, resulting in gradually progressive endothelial damage, microvascular thrombosis, and parenchymal necrosis. Pathologic grading schemes have been developed regarding the extent to which AR involves vascular damage, cellular infiltration, or a combination of both. Vascular AR is thought to be mediated by the presence of DSAs, albeit not in sufficient numbers to cause HAR. C4 d, a complement split product detected immunohistochemically in the capillaries of biopsied graft specimens, is highly correlated with AMR [9]. Without intervention, AR inevitably progresses to graft loss. The clinical presentation of AR varies markedly, depending on the specific organ, on the level of immunosuppression, and on the attendant reduction of inflammation in the affected tissues.

Unless the host immune system is suppressed pharmacologically, a transplant inevitably leads to AR. A combination of immunosuppressive agents is typically used chronically to prevent AR, including a lymphocyte antagonist (usually a calcineurin inhibitor [CNI] such as cyclosporine or tacrolimus) and an antiproliferative agent (such as azathioprine or mycophenolate mofetil), with or without corticosteroids. Antilymphocyte antibody therapy is often added during induction of immunosuppression or for treatment of "steroid-resistant" AR.

In the last decade, immunosuppression for transplant recipients has been undergoing a paradigm shift. Since the mid-1990s, the use of antibody induction in solid-organ transplant recipients has increased from 25% to more than 60% [10]. In particular, monoclonal antibodies such as basiliximab and daclizumab (both anti-CD25 [IL-2 receptor]) as well as alemtuzumab (Campath-1 H, anti-CD52) were proven to be effective induction agents in preventing AR in renal or pancreas transplantation [11–13]. Furthermore, strategies such as corticosteroid avoidance and CNI-reduced or CNI-free maintenance immunosuppression were shown to be equivalent to traditional triple-drug maintenance [14–16]. Nonetheless, all immunosuppressive agents carry some risk of toxicity and adverse reactions that may complicate therapy (Table 186.2).

Chronic Rejection

CR remains a common yet poorly understood clinical problem, with slightly different manifestations in each type of graft. Over time, the accumulation of microvascular injury in a graft degrades graft function, with eventual graft loss. This process appears to be mediated by multiple mechanisms, likely including both immune and nonimmune factors. Evidence for the contribution to CR of immune factors includes the observation that AR episodes significantly increase the likelihood of CR as well as the correlation, observed in renal transplant recipients, between a poor response to AR treatment and the subsequent development of CR [17]. A similar association between a poor response to AR treatment and the subsequent development of CR has been observed in liver transplant recipients, although reversible AR has little impact. Nonimmune factors likely also contribute to the development and progression of CR, including the toxic effects of immunosuppressive medication and cumulative injury from infection such as that caused by cytomegalovirus (CMV) [18] and polyomavirus [19]. CR nearly always eventuates in graft loss, although the rapidity of the process varies considerably.

Renal Grafts

Current reports indicate that about 10% to 25% of renal transplant recipients experience an episode of AR. Because most episodes are clinically silent, the diagnosis of AR must be considered in recipients whose serum creatinine, blood urea nitrogen, and urinary output values have normalized and whose graft function has been stable in the outpatient setting, but whose serum creatinine and blood urea nitrogen values subsequently rise while their urinary output decreases. The presence of hypovolemia, drug nephrotoxicity (e.g., high calcineurin levels), ureteral obstruction or leak, lymphocele, or vascular anastomotic complications should be excluded, and the diagnosis of

TABLE 186.2

IMMUNOSUPPRESSIVE MEDICATIONS, MECHANISMS OF ACTION, AND COMMON SIDE EFFECTS

Medications	Mechanisms of action	Side effects
Corticosteroids	Upregulate IκB Decrease IL-1, TNF-α, IFN-γ Exert anti-inflammatory effect	Cushing syndrome
Azathioprine	Act as an antimetabolite	Marrow suppression GI, liver toxicity
Mycophenolate mofetil	Specifically affect lymphocytes Act as an antimetabolite	Marrow suppression GI intolerance
Cyclosporine	Act as a calcineurin inhibitor Downregulates IL-2	Nephrotoxicity Neurologic symptoms
Tacrolimus (FK506)	Calcineurin inhibitor Downregulate IL-2, IFN-γ	Nephrotoxicity Neurotoxicity Diabetogenic
Sirolimus (rapamycin)	Block IL-2R, IL-4, IL-6, platelet-derived growth factor signaling	Impaired healing Hypertriglyceridemia
Antilymphocyte globulin	Act as a cytolytic antibody Block and deplete T cells	Leukopenia Thrombocytopenia "Serum sickness"
OKT3	Act as a cytolytic antibody Block T-cell receptor Deplete T cells	Cytokine release Aseptic meningitis
Daclizumab (or basiliximab)	Blocks IL-2R Inhibit T-cell activation	Minimal impact

GI, gastrointestinal; IFN, interferon; IL, interleukin; OKT3, ornithine–ketoacid transaminase-3.

AR should be established via histologic examination of a percutaneous graft biopsy specimen. Rarely, tenderness and swelling in the area of the graft occur, and occasionally fever or other signs of systemic inflammation, although such findings used to be common.

As discussed earlier, most AR episodes occur in the early posttransplant period. Among the subset of recipients who experience delayed graft function, up to 30% exhibit evidence of AR on biopsy [20]; 20% of recipients who require dialysis posttransplant have AR [21]. Intriguingly, up to 30% of recipients with well-functioning grafts also have AR, per early posttransplant protocol biopsies, but whether such findings are clinically important and whether mild episodes should invariably be treated remain controversial [22]. Recent studies have provided data that may allow prediction of individual risk of AR, with the potential for individualizing immunomodulatory therapy. For example, donor IL-6 genetic polymorphism is strongly associated with an increased incidence of AR posttransplant [23], and recipients with elevated levels of serum C-reactive protein (CRP), presumably indicative of systemic inflammation, have a higher rate of AR and a shorter time to AR than those with lower CRP levels [24]. Other biomarkers (such as soluble CD30, gene expression assays on peripheral blood samples, urinary proteomics, and T-lymphocyte subset analysis) were shown to be predictive for rejection or transplant tolerance, and are currently undergoing various clinical investigations [25].

The diagnostic workup for AR includes studies that may identify alternative causes of recipient graft dysfunction (Table 186.3). It is vital to consider alternative diagnoses, particularly in the early postoperative period, including vascular problems with the arterial or venous anastomoses, ureteral obstruction, or urinary leak. Other common causes of apparent graft dysfunction include the acute tubular necrosis associated with delayed graft function, hypovolemia and attendant prerenal azotemia, and the nephrotoxic effects of cyclosporine and tacrolimus. To rule out the vascular and ureteral problems discussed previously, a duplex ultrasound study of the renal graft is commonly obtained. Several ultrasound findings may suggest the diagnosis of AR: increased size of the graft, increased cortical thickness, enlargement of the renal pyramids, and decreased

TABLE 186.3

BASIC WORKUP OF RECIPIENTS WITH GRAFT DYSFUNCTION OR ACUTE REJECTION

History and physical examination	Establish and order differential diagnosis
Doppler ultrasound	Rule out vascular surgical complication Rule out leak (e.g., biliary, ureteral)
Serum chemistry	Evaluate relative blood urea nitrogen and creatinine, amylase, bilirubin Detect and treat electrolyte abnormalities
Drug levels	Evaluate for potential drug toxicity Detect inadequate drug levels
Blood cell count, cultures	Evaluate for potential infection
Graft biopsy	Firmly establish and grade graft rejection

graft renal artery blood flow [26]. The diagnosis of AR is clearly established by percutaneous allograft biopsy and histologic examination. Biopsy is generally safe when performed by experienced practitioners; however, complications include bleeding, hematoma and arteriovenous fistula formation, and ureteral or major vascular injury.

Rejection is graded according to a standardized histologic classification scheme, the modified Banff Criteria, which may be used to guide therapy [27]. Fine-needle aspiration biopsy has been used by some centers to establish the diagnosis of AR; however, some consider the loss of microstructural data, as compared with traditional core biopsy, to be a weakness of the technique. In particular, the diagnoses of acute vascular rejection and CR are difficult to make using fine-needle aspiration biopsy.

The treatment of AR in renal transplant recipients varies between centers. High-dose methylprednisolone (500 to 1,000 mg per day or every other day [2 to 3 doses] is common) is often the initial approach. Corticosteroid-resistant AR, or AR that is histologically graded as severe or vascular, is often treated with potent depleting antilymphocyte antibodies such as murine monoclonal IgG2a antibody (OKT3) or polyclonal antithymocyte globulin (antithymocyte gamma globulin, Thymoglobulin). Alemtuzumab was selectively used to treat AR in some centers [28]. Since some AR episodes occurred while the recipients were on stable immunosuppression, their maintenance therapy was switched from cyclosporine to tacrolimus or from azathioprine to mycophenolate mofetil. Most AR episodes are reversible with current therapies; however, as noted previously, the long-term outlook for preservation of graft function is lessened with each episode, especially when the posttreatment serum creatinine level does not return to the pre-AR baseline.

CR in renal transplant recipients is a persistent clinical problem and appears to be multifactorial, with immunologic and nonimmunologic factors driving the gradual loss of graft function. As described earlier, minimizing the frequency and severity of AR episodes is important in decreasing the likelihood of eventual CR. Nonimmunologic factors thought to contribute to CR include (a) episodes of infection, particularly due to CMV and BK virus (*vide infra*); (b) the nephrotoxicity of CNI therapy; (c) ischemia-reperfusion injury and delayed graft function in the peritransplant period; and (d) innate cell senescence within the graft [29]. Attention is being directed toward identifying inflammatory activity within the graft, in response to both immune and nonimmune insults that may contribute to the development of CR. One of the leading causes of kidney retransplants is CR. It remains a formidable problem that is still poorly understood.

Hepatic Grafts

The hepatic graft is considered to be immunologically "privileged" in that evidence of some degree of immune tolerance occurs in a substantial number of liver transplant recipients over time. Despite that observation, all forms of rejection can occur posttransplant. At one time, it was thought that HAR did not occur in the hepatic graft; this idea is now known to be incorrect, as anti-HLA antibody-mediated HAR has been described in liver transplant recipients [30,31]. Unlike the renal graft, the hepatic graft undergoes HAR over a number of days, not minutes to hours, probably secondary to its ability to absorb a large amount of antibody before the onset of the significant microthrombosis and vascular damage seen in HAR. A more delayed form of antibody-mediated rejection is seen in up to 33% of patients who undergo liver transplants across ABO-incompatible blood groups [32], but even this barrier appears surmountable with the use of plasmapheresis along with aggressive immunosuppression [33].

AR remains an important clinical problem in liver transplantation; even with the use of standard multiagent immunosuppression, the incidence of AR ranges from 30% to 80%. In two large, multicenter trials, double therapy with a CNI and steroids resulted in a 60% to 80% incidence of AR [34,35]. Triple therapy with Neoral® or Sandimmune®, along with azathioprine and prednisone, resulted in a 30% to 45% incidence of AR [36]. Substitution of mycophenolate mofetil for azathioprine further reduced the incidence of AR to 26% [37]. The latest liver transplant regimen, consisting of two doses of a monoclonal anti-IL2 receptor (basiliximab) as induction therapy and dual maintenance therapy with a CNI and mycophenolate mofetil, was shown to lessen the severity of rejection without increase the infection rate [38,39].

The diagnosis of AR in liver transplant recipients is normally suggested by elevated levels of transaminases, bilirubin, or alkaline phosphatase. Among patients with T-tube drainage (which is increasingly uncommon), the biliary drainage may be seen to thicken, darken, and decrease in amount. The suspicion of AR mandates graft biopsy and studies to eliminate other possible causes of early hepatic graft failure. Duplex ultrasonography and, in some cases, cholangiography are increasingly being replaced by magnetic resonance imaging. Biopsy findings are classified, according to a standardized set of criteria, as *mild*, *moderate*, and *severe*, with clear implications for prognosis [40]. AR is normally treated with high-dose corticosteroids, but 5% to 10% of cases are steroid-resistant; such recipients are then treated with an antilymphocyte antibody. Interestingly, in large population studies, the incidence of AR is associated with improved long-term patient survival rates [41], albeit thought to be due to the higher incidence of AR in younger, healthier recipients. Even adjusting for recipient characteristics, AR has not been clearly associated with either decreased graft or patient survival rates; however, frequent AR episodes are a risk factor for subsequent CR, so continued pursuit of immunosuppressive strategies that reduce the risk of AR is imperative.

CR in liver transplant recipients is characterized by vascular obliteration and bile duct loss ("the vanishing duct syndrome"). Seen in 5% to 10% of recipients, it is more common in those with vasculitic findings during AR episodes; if larger vessels are not seen on biopsy, the diagnosis of CR may be misread as AR. The incidence of CR appears to be decreasing, perhaps as a result of changes in immunosuppressive regimens [42]. In addition to multiple AR episodes, other factors associated with an increased risk of CR include CMV infection, chronic hepatitis, increased donor-recipient histocompatibility differences, and increased ischemia time. CR does not always herald graft loss; long-term patient survival and even regeneration of bile ducts have been described. Tacrolimus has been used to salvage grafts in recipients with CR on cyclosporine-based immunosuppression, with a 73% success rate [43].

Pancreas Grafts

At most centers, patients undergoing a pancreas transplant alone or a simultaneous pancreas–kidney transplant receive more potent immunosuppression than do renal transplant recipients, thanks to initial studies demonstrating a higher rate of AR after those two types of pancreas transplant [44]. Overall success rates continue to improve: the risk of AR has been reduced by standardized induction therapy with antilymphocyte antibody preparations, and it may be further reduced with mammalian target of rapamycin (mTOR) inhibitors and/or with IL-2 receptor monoclonal antibodies [45].

Establishing the diagnosis of AR in pancreas transplant recipients may be difficult. Hyperglycemia is a late finding that only occurs with substantial loss of functional islet-cell mass.

By the time hyperglycemia is seen, it may be too late to retain a functional graft. Clinical findings may include fever and graft tenderness; however, pancreas graft rejection is often clinically silent.

For pancreas grafts transplanted along with a renal graft, a rising creatinine level is often used as a surrogate marker of rejection, with antirejection therapy aimed at both the pancreas graft and the renal graft. However, isolated pancreas graft rejection is observed in up to 20% of simultaneous pancreas–kidney transplant recipients who have AR [46].

In pancreas transplant recipients with exocrine bladder drainage, a decreasing urinary amylase level may be used as a marker of graft rejection [47]. Other possible markers of rejection (serum anodal trypsinogen, serum amylase, soluble HLA, and analysis of glucose-disappearance kinetics during a brief glucose tolerance test) have been examined but have failed to gain wide acceptance.

The diagnosis of pancreas graft rejection is confirmed by biopsy, which may be performed percutaneously or, in bladder-drained recipients, through a cystoscopic, transduodenal approach. Complications (bleeding, arteriovenous fistula formation, graft pancreatitis) have been described, but most biopsies do not lead to complications. Pancreas transplant recipients with early evidence of graft dysfunction should undergo Doppler ultrasonography to rule out graft thrombosis, which occurs in up to 10% to 20% of them [48].

Treatment of AR for pancreas transplant recipients is similar to that for renal or liver transplant recipients. High-dose corticosteroids are given initially, but a low threshold is maintained for possibly switching to antibody-based therapy, given the relatively common steroid resistance. Most AR episodes are reversed with treatment.

Cardiac Grafts

Rejection in heart transplant recipients is a major obstacle to long-term success and accounts for up to a third of the deaths. All forms of rejection are seen in heart transplant recipients. Albeit rare, HAR due to preformed antigraft antibodies occurs within minutes to days; it manifests with rapid deterioration of cardiac function, with prolonged need for inotropic support. In recipients whose grafts fail to recover rapidly, an attempt to reverse HAR by plasmapheresis may be made, but success is uncommon, and an immediate retransplant is usually required.

AR in heart transplant recipients is common and usually occurs in the first 3 to 4 months posttransplant. At one time, the diagnosis was made on the basis of the development of congestive heart failure or the elaboration of electrocardiographic abnormalities. However, the present-day use of protocol endomyocardial biopsies has eliminated such late findings of AR, except in noncompliant recipients. Most centers use frequent percutaneous transjugular right ventricular endomyocardial biopsies as part of a standardized surveillance protocol. Biopsies are evaluated histologically, according to an international grading system [49], and therapy is directed accordingly.

Several investigators have developed noninvasive approaches to establishing the diagnosis of AR, including electrocardiographic frequency analysis, nuclear scintigraphic techniques, and echocardiography; however, no approach has attained sufficient sensitivity to eliminate the need for protocol biopsies. The need for continued endomyocardial biopsies later than 1 year posttransplant is controversial, and many centers discontinue performance of biopsies at 1 year unless indicated on clinical grounds.

The treatment of AR is based on histologic findings. Bolus steroid therapy is used in lower-grade rejection without hemodynamic compromise; oral prednisone therapy for mild AR also has been used with success [50]. Salvage therapy with an antilymphocyte antibody agent is most common in recipients with histologic findings of more severe rejection, in recipients with steroid-resistant rejection, and in recipients with signs of hemodynamic compromise. In a series of 100 of such high-risk recipients, AR was reversed in 90% of those treated with 10 to 14 days of OKT3 [51]. However, other investigators have had markedly lower rates of success with OKT3 in the treatment of steroid-resistant rejection [52]. Methotrexate also has been used to reverse AR that fails to respond to steroids or that is refractory to OKT3.

Other approaches include switching from cyclosporine-based to tacrolimus-based immunosuppression as rescue therapy in recipients with refractory AR, a strategy that was proved to be safe and efficacious [50]. Photopheresis has been used in the treatment of recipients with T-cell lymphoma and autoimmune disease. Studies of photopheresis and triple-drug immunosuppression have provided evidence of a decrease in the total number of AR episodes, as compared with triple-drug immunosuppression alone [50]. Of note, photopheresis has reversed refractory high-grade rejection in small numbers of heart transplant recipients [53].

CR manifests in heart transplant recipients as cardiac allograft vasculopathy (CAV), an entity that is the major cause of late-term morbidity and mortality. The pathologic findings of CAV include progressive intimal thickening in a concentric manner, which begins distally within the cardiac vasculature. It is associated with the loss of response to endogenous (and pharmacologic) vasodilators [50]. CAV is thought to be immunologically mediated, because HLA donor-related matching is clearly associated with reduced rates of CAV [54]. Nonimmunologic mechanisms are also thought to be involved; identifiable risk factors for CAV include hyperlipidemia, donor age older than 25 years, recipient weight gain, CMV disease, preexisting donor or recipient coronary artery disease, and increasing time posttransplant [50]. Another nonimmunologic risk factor for CAV is ischemic time during the peritransplant period. As in other solid-organ transplant recipients, the use of mycophenolate mofetil is associated with a reduction in the incidence of CR in heart transplant recipients [55].

Lung Grafts

The lung graft is highly prone to rejection—nearly all lung transplant recipients experience at least 1 AR episode. The clinical difficulty posed by rejection is in distinguishing it from other causes of decreased graft function, most commonly infection.

HAR of the lung graft [56] is mediated by recipient preformed antibodies to the donor graft, in a fashion similar to other organs. The clinical manifestation is similar to the more common ischemia-reperfusion injury, which, unlike HAR, usually resolves. HAR of the lung graft is rare and only described in case reports. To date, we know of no lung transplant recipients who have survived HAR. It must be prevented via initial cross-match testing and exclusion of immunologically unsuitable donor organs.

Most AR episodes occur during the first 3 to 6 months posttransplant. Some recipients experience symptoms, including fever, cough, and dyspnea, but many are asymptomatic. Early diagnosis of AR in lung transplant recipients is essential: untreated AR can lead to respiratory insufficiency or failure, and repeated AR episodes are associated with an increased risk of bronchiolitis obliterans and eventual graft failure [57].

The diagnosis of AR is made by transbronchial biopsy, although less invasive techniques continue to be assessed [58]. Bronchoalveolar lavage (BAL) is also performed to rule out

infection before increasing immunosuppression; infection and rejection may occur simultaneously in up to 25% of lung transplant recipients with AR [59]. Early diagnosis of AR may be aided by spirometry; decreases in timed forced expiratory volume, in pulmonary capillary blood volume, and in the diffusing capacity of the lungs for carbon monoxide are associated with AR and should prompt investigation. Radiography is not ordinarily helpful. The histologic findings of AR include lymphocytic infiltrates into the perivascular and interstitial spaces; AR is graded according to histologic findings [60].

The initial treatment of AR in lung transplant recipients typically entails high-dose corticosteroids; if they are not successful, anti–T-cell antibody therapy is tried next. Many recipients initially respond to the steroid pulse therapy, yet it may not completely clear their AR, and secondary episodes are common, so additional therapy may be required. For that reason, surveillance bronchoscopy with transbronchial biopsies and BAL are common after initial treatment [61].

CR in lung transplant recipients is extremely common, affecting up to 40% of recipients at 2 years posttransplant and up to 70% of recipients after 5 years [62]. The mean time to diagnosis of graft dysfunction posttransplant is 16 to 20 months. A definitive histologic diagnosis of early bronchiolitis obliterans may be difficult to obtain, so it must be established largely on clinical grounds. Radiography, again, is not specific. Typical presenting symptoms are cough, progressive dyspnea, and loss of exercise tolerance. The use of home spirometry can point to the diagnosis based on a 20% reduction in timed forced expiratory volume on successive measurements [63]. Factors associated with accelerated bronchiolitis obliterans include multiple episodes of AR, CMV pneumonitis/infection, *Pneumocystis jiroveci* pneumonia (PCP), and episodes of airway ischemia [62,64].

Many different therapies have been tried for recipients with bronchiolitis obliterans, but with little success. Increases in immunosuppression, antilymphocyte antibody therapy, and inhaled cyclosporine have all been tried. Ultimately, the progress of bronchiolitis obliterans is inexorable, with continued loss of graft function and subsequent death. A lung retransplant is the only viable option [65].

INFECTIONS

The suppression of the host immune response is required to establish and maintain a functioning solid-organ graft. The development of immunosuppressive therapies has been impressive, leading to the widespread use of solid-organ transplantation as the primary therapy for a number of organ failure syndromes. This success comes at a price, however, and the successful immunosuppression that allows engraftment leaves the host with an increased susceptibility for a number of serious infectious complications. Up to 80% of solid-organ transplant recipients experience an infectious complication during the first year posttransplant, and infections remain a major cause of morbidity and mortality in the transplant population [66].

The range of potential pathogens that can cause disease in the immunosuppressed host is prodigious. Not only are the common endogenous and nosocomial flora involved, but also "opportunistic" or "atypical" pathogens must be considered in the differential diagnosis of a solid-organ transplant recipient who has evidence of infection. In considering the epidemiology of infectious complications posttransplant, the clinician must assess several factors, including the time posttransplant, the organ transplanted, the type and degree of immunosuppression, the need for antirejection therapy, and the potential occurrence of surgical complications.

The greatest risk of infections corresponds with the period of most intense immunosuppression, which is characteristically during the first 6 to 12 months posttransplant and after antirejection therapy, particularly for repeated AR episodes. Rubin et al. have characterized periods posttransplant during which certain infection patterns may be seen [67]. Infectious complications in the first month posttransplant are typically caused by endogenous or nosocomial flora that would cause disease in an immunocompetent host [68], including (a) bacterial surgical site infections; (b) postoperative or ventilator-associated pneumonia; (c) urinary tract infections (UTIs) associated with prolonged indwelling urinary catheters; (d) intraabdominal infections related to surgical complications; and (e) central venous catheter infections [67,68].

The period between 1 and 6 months posttransplant is typically the time of greatest immunosuppression and, subsequently, the time most opportunistic infections occur. They are frequently caused by fungal or especially viral pathogens that may become activated after lying dormant in the host or may be transferred from the donor with the graft [69,70]. Knowledge of the characteristic patterns of maximal frequency for a number of specific viral pathogens within that 5-month window may be helpful to the clinician in establishing the diagnosis [71].

These infection patterns may be categorized into an *early cluster* of viral agents occurring with peak frequency between 2 and 3 months posttransplant and a *late cluster* more commonly occurring between 4 and 9 months posttransplant. The early cluster includes CMV, adenoviruses, hepatitis B virus (HBV) and hepatitis C virus (HCV), and human herpes virus (HHV)-6 [67–69,71–74]. The late cluster includes varicella zoster and polyoma viruses [19,75]. Epstein–Barr virus (EBV) may cause disease throughout the first year posttransplant [76].

The opportunistic fungi can similarly be observed to cluster with *Candida* and *Aspergillus* species (spp), causing infections in the first 2 to 3 months posttransplant [77,78], whereas *Cryptococcus*, histoplasmosis, coccidioidomycosis, and *P. jiroveci* most often occur later during the first year [79,80].

After the first 6 to 12 months, most transplant recipients exhibit patterns of infectious disease morbidity that are similar to those of the general population, with frequent respiratory infections secondary to pneumococcal infections and influenza, as well as uncomplicated UTIs. However, opportunistic infections can occur anytime. Increased immunosuppression secondary to AR treatment may slightly increase transplant recipients' susceptibility to, and alter the temporal pattern of, various pathogens. When assessing immunosuppressed transplant recipients for infectious diseases, the clinician must maintain a high index of suspicion at all times. The typical localizing signs of infection and inflammation may be blunted, or even absent, because of the anti-inflammatory action of immunosuppressive regimens.

An important component of the solid-organ transplant process is the preoperative assessment of both the recipient and the donor for any underlying infections, or any disease processes that predispose to infections, that could manifest subsequent to administration of exogenous immunosuppression. For the donor, the most important evaluation is the determination of CMV and EBV status, because those two agents are most easily transmitted to a seronegative recipient. Cultures of organ preservation fluid are routinely positive, but appropriate antiviral therapy can ordinarily prevent positive cultures from causing clinically significant disease [81]. For the recipient, a thorough pretransplant history and physical examination are essential to minimize the risk of infectious complications secondary to a latent or indolent infectious process. Routine viral studies should be obtained, vaccinations updated, and prophylaxis administered where indicated (e.g., gut decontamination in liver transplant candidates with end-stage liver disease or prophylactic antibiotics in patients with cystic fibrosis).

Bacterial Infections

In the first 30 days posttransplant, bacterial infections are common. Even in the immunocompetent patient population, bacterial infections are common complications of surgery. The risk of a nosocomial bacterial infection is related to the site of surgery as well as to the continued presence of any catheters, lines, endotracheal tubes, or other breaks in the skin. The most common sites of infection are the urinary tract, the surgical site, the lungs, and the bloodstream. The risk of nosocomial bacterial infections is directly related to host factors (including underlying diseases such as diabetes or cirrhosis, obesity, and chronic pulmonary disease) as well as to technical and management factors (including the length and technique of the operation, the development of a hematoma or seroma, and the need for prolonged urinary catheterization, mechanical ventilation, or central venous catheterization).

Particularly in renal transplant recipients and in bladder-drained pancreas transplant recipients, the urinary tract is a common site of bacterial infections. Bacteriuria may be detected in up to 83% of renal transplant recipients [82], with an attendant increased risk of systemic sepsis and wound infection. The most common pathogens are Gram-negative aerobes, enterococci, and *Candida* spp. The risk factors associated with an increased incidence of UTIs include prolonged catheterization, hemodialysis, and antibiotic prophylaxis in excess of 48 hours [83]. The use of ureteral stents in renal transplant recipients, though it may help reduce ureteral complications, is associated with an increased rate of UTIs [84]. The use of prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) is common in renal transplant recipients, primarily to decrease the risk of UTIs. Long-term prophylaxis helps reduce the incidence of infections due to several opportunistic pathogens, including *P. jiroveci*, *Toxoplasma gondii*, *Listeria monocytogenes*, and *Legionella pneumophila* [85].

Diagnosis of a UTI in transplant recipients is based on clinical suspicion and on urinalysis and culture results. The typical findings of dysuria, hesitance, and frequency may be absent; the only clinical manifestations might be a minimal fever or an elevated white blood cell count. Treatment is often empiric and, because of the risk of bacteremia, should consist of intravenous administration of a third-generation cephalosporin or a quinolone, particularly during the first months posttransplant. Once the causative microbe has been identified and antimicrobial sensitivity data are available, treatment can be refined.

In recipients of solid-organ grafts besides the kidney and bladder-drained pancreas who do not require a long duration of urinary catheterization, an increased risk of bacterial or fungal UTIs is not seen.

Infections of the surgical site are potentially a source of major morbidity and, occasionally, graft loss and mortality in solid-organ transplant recipients. Surgical site or wound infections are classified according to the structures involved. Infections above the fascia are superficial, infections below the fascia are deep, and combined infections involve elements of both the superficial and the deep compartments of the wound [68].

In all solid-organ transplant recipients, immediately before their operation begins, a single dose of an antibiotic should be administered, to decrease the risk of surgical site infections. In pancreas, bowel, lung, and liver transplant recipients, significant degrees of wound contamination may occur, so antibiotics are typically administered for 24 to 72 hours posttransplant, although data to support that practice are lacking. In renal transplant recipients, the surgical site infection rate is very low (1% to 2%) and is comparable to the wound infection rate for other clean-contaminated procedures in immunocompetent patients [86].

However, other transplant procedures are associated with higher rates of infection. The wound infection rate after heart transplants is typically below 8%, which is comparable to the rate for other high-risk cardiac procedures [87]. The rate of wound infections is slightly higher after lung and heart–lung transplants [88]. The rate after liver transplants of superficial wound infections is 6% to 8%; of deep wound infections (most commonly an intra-abdominal abscess secondary to a biliary leak), 15% to 20% [69]. The rate of wound infections after pancreas transplants is high: 10% to 40%, superficial; 15% to 22%, deep; and 8%, combined [89]. Such wound infections confer substantial morbidity, are associated with mortality in some cases, and require a very aggressive approach to diagnosis and therapy.

Pathogenic microbes are predictable, according to the type of operation. In renal transplant recipients, wound infections are caused by the endogenous flora of the skin (Gram-positive aerobes) and the bladder (Gram-negative aerobes), with occasional *Candida* spp and enterococci.

In heart transplant recipients, wound infections are almost invariably due to skin flora such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, although some fungal and atypical pathogens are found.

Lung transplants introduce respiratory flora and the potential for grave infections with *Pseudomonas aeruginosa*.

In liver transplant recipients, wound infections are typically associated with either skin or biliary flora, although any preexisting cirrhosis and end-stage liver disease may result in colonization with drug-resistant nosocomial pathogens.

In pancreas transplant recipients, wound infections are invariably polymicrobial, with gram-positive, fungal, and resistant Gram-negative pathogens frequently present. Treatment generally requires opening of the wound, reexploration, and/or administration of broad-spectrum antimicrobial therapy (with a carbapenem or extended-spectrum penicillin, a β-lactamase inhibitor, and vancomycin) and often antifungal coverage.

Wound infections are often subtle, and findings may be limited to fever, elevated white blood cell count, or wound drainage with a deceptively innocuous appearance. Any wound drainage should be examined by Gram stain and culture; any suspicion or evidence of infections should result in opening of the superficial wound. Additionally, imaging should be undertaken to rule out infections in the deep surgical space; if a fluid collection is identified, percutaneous drainage or prompt exploration is needed. Prolonged, broad-spectrum antimicrobial therapy is used, and immunosuppression is minimized in the face of potentially life-threatening infections.

The development of postoperative pneumonia varies with the type of transplant and is associated with a high mortality rate (20% to 60%) [90]. Renal transplants are associated with the lowest incidence of postoperative pneumonia (1% to 2%); lung transplants, the highest (22%). The most common pathogens are Gram-negative aerobes, staphylococci, and *Legionella* spp. Frequently, *Candida* spp or CMV may be identified along with bacterial pathogens, particularly in the first 2 to 3 months posttransplant. Such findings are clinically significant, and active CMV pneumonitis is a significant risk factor for the development of bacterial pneumonia [90,91].

Several risk factors may predispose solid-organ transplant recipients to the development of pneumonia, including prolonged mechanical ventilation, thoracic surgery, pulmonary edema, and intense immunosuppression or AR treatment. Lung transplant recipients are at increased risk, because of their lungs' preexisting colonization with endogenous flora as well as the loss of the mucociliary clearance function associated with denervation [88]. Those with cystic fibrosis have an additional risk, because their lungs and sinuses are universally colonized with highly drug-resistant flora such as *Pseudomonas aeruginosa* and *Burkholderia cepacia* [92]. The evaluation of

suspected pneumonia in lung transplant recipients should be thorough, including bronchoscopy with biopsies and BAL to rule out rejection, as described above. Pleural effusions should be drained and cultured, because the progression of an infected effusion to empyema in lung transplant recipients is associated with a very high mortality rate.

Bacteremia in the transplant population, as in the general hospital population, may occur secondary to seeding along a vascular access device or as a result of hematogenous spread from another source; or, it may be primary (without a source being identified). UTIs, wound infections, and pneumonia are risk factors for the development of bacteremia, as is prolonged vascular catheterization. Additional risk factors include receiving a deceased donor graft, leukopenia, and antirejection therapy. Bacteremia in immunosuppressed patients may present as fever, leukocytosis, leukopenia, or hypotension without other significant manifestations. Consequently, routine blood cultures should be part of any workup for fever in this population. Suspicion of bacteremia should prompt removal and culture of intravascular devices and a search for a source of other sites of infection. The mortality rate of bacterial sepsis and septic shock in transplant recipients exceeds 50%. Consequently, the use of broad-spectrum antimicrobial therapy, an aggressive approach to source control, and the minimization of immunosuppression are indicated.

Several atypical bacterial infections occur in the solid-organ transplant recipients, including mycobacteria such as *Mycobacterium tuberculosis*, *Nocardia* spp, and *Listeria monocytogenes*. Such infections are associated with high rates of morbidity and mortality. Mycobacterial infections are 50 to 100 times more frequent in the transplant population than they are in the general population and are fatal in 30% of cases. Most mycobacterial infections occur within the first 6 to 12 months posttransplant and are associated with intense immunosuppression and antirejection therapy [93]. Infections are typically due to reactivation of latent disease or transmission with the transplanted graft. Their diagnosis is complicated by the typical lack of reaction to skin testing seen with immunosuppression. Consequently, a high index of clinical suspicion is needed. If mycobacterial pulmonary infection is suspected bronchoscopic evaluation with biopsy, acid-fast staining, and culture should be performed. Treatment consists of multidrug therapy with isoniazid, ethambutol, pyrazinamide, and rifampin. Prophylaxis should be considered in patient populations in whom infections are common, in patients with a history of significant exposure without subsequent therapy, and in patients with a history of serious or inadequately treated infections.

Nontuberculous mycobacteria (NTM) such as *Mycobacterium avium complex*, *M. ulcerans*, and *M. xenopi* are environmental mycobacteria that rarely caused disease in humans until the AIDS epidemic two decades ago. NTM infections typically manifest as insidious pulmonary or soft tissue infections in immunosuppressed patients. If NTM infections are suspected, repeat isolations by bronchoscopy or tissue biopsy are required to improve the chance of diagnosis. In addition to acid-fast staining, a special culture for an atypical mycobacterium should be obtained. Besides long-term antimicrobial treatment, wide debridement of the infected site is often required to eradicate such infections [94].

Listeria monocytogenes infection may be associated with pneumonia, bacteremia, or, most ominously, cerebromeningitis in the transplant population. In renal transplant recipients, *Listeria* spp have been associated with a 26% mortality rate. Consequently, if listeriosis (pulmonary or meningitis) is suspected in any immunosuppressed patients, a thorough evaluation must be performed. Empiric therapy for meningitis should include appropriate coverage, such as ampicillin plus an aminoglycoside [95]. The extended-spectrum penicillins also provide adequate coverage.

Nocardial infections most commonly manifest with pulmonary symptoms and signs, but disseminated disease may involve the skin, eyes, and brain, alone or in combination. The clinical manifestations are nonspecific and comprise fever, chills, malaise, occasional cough, dyspnea, headache, or mental status change. Such infections have a mortality rate of 25% to 50% and must be aggressively diagnosed and treated [96]. The diagnosis is made by microscopic examination of sputum or lung (or occasionally brain) biopsy tissue, or by aspiration of a skin nodule using routine, Kinyoun, and Ziehl-Neelsen staining. Treatment consists of high-dose intravenous TMP-SMX, generally in combination with an aminoglycoside, such as amikacin, with continued treatment with oral TMP-SMX, preferably for life. Concurrently, immunosuppression should be curtailed, particularly during treatment of aggressive, disseminated infections.

Fungal Infections

Solid-organ transplants are associated with a significant risk of fungal infections. In the era of broad-spectrum antibacterial prophylaxis and empiric therapy, the incidence of fungi as pathogens is increasing, as is the incidence of azole drug-resistant fungal infections. Fungal infections are most common after liver and pancreas transplants, for which the incidence approaches 40% [97]. But they are less common after renal transplants (only 5%). Nonetheless, all fungal infections are serious infections, with an attendant mortality rate, associated with invasive disease, of 30% to 50%. As described previously, most fungal infections occur during the first 3 to 4 months posttransplant, when immunosuppression is greatest. The source of most fungal pathogens is the oral cavity, the gastrointestinal (GI) tract, or the environment.

The most common fungal pathogens are the *Candida* spp [98]. Candidal overgrowth of the oral and GI tract is common, and prophylaxis consisting of topical nystatin or clotrimazole is often used. Risk factors associated with invasive candidal disease include diabetes, neutropenia, intense immunosuppression, and prolonged administration of antibacterial antibiotics, particularly broad-spectrum agents. Long-term TMP-SMX prophylaxis has not been associated with fungal infections. Despite prophylaxis, invasive candidiasis does occur, most often in transplant recipients with a perforation of the GI tract, an anastomotic breakdown, a deep surgical-site infection, or a concomitant GI infection, such as CMV gastroenteritis or colitis.

Increasing use of triazoles such as fluconazole has led to more frequent isolation of resistant *Candida* species, such as *C. glabrata* and *C. krusei*. Even apart from this observation, most invasive candidal infections should be treated with amphotericin B or the newer agents like echinocandins (see later), because of the attendant morbidity and mortality in the immunosuppressed population [99]. Caspofungin is an echinocandin that acts to block the synthesis of 1,3-β-d-glucan, an essential element of the fungal cell wall. It is well tolerated, with a side effect profile that compares favorably to amphotericin B. Note that caspofungin and amphotericin B appear to act in an additive manner, and cross-resistance has not been identified [100]. Clinical trials of caspofungin versus amphotericin demonstrated equivalent outcomes in the treatment of candidemia [101]. In solid-organ transplant recipients, caspofungin will be an important drug in treating serious fungal infections, particularly because it lacks the nephrotoxicity of amphotericin. Two of the more recently released triazole drugs, itraconazole and voriconazole, also possess activity in vitro against *Aspergillus* spp; the combination of voriconazole and caspofungin has been shown to enhance clinical efficacy [102].

Aspergillosis occurs in 1% to 4% of transplant recipients, most commonly after liver and lung transplants. Half of such patients go on to develop disseminated disease, with a mortality rate in excess of 80% [78,103]. Most patients with aspergillosis present with what appears to be a bacterial pneumonia. In high-risk lung or liver transplant recipients, or in lower risk patients whose supposed pneumonia fails to respond to appropriate antibiotic therapy, an aggressive diagnostic approach is warranted. The diagnosis of aspergillosis is established initially by microscopic examination of samples obtained via bronchoscopy and BAL for the presence of filamentous hyphae. Agents approved by the U.S. Food and Drug Administration (FDA) against invasive aspergillosis include liposomal amphotericin B, itraconazole, voriconazole, posaconazole, and caspofungin. Dissemination to the central nervous system (CNS) may result in brain abscesses, which in the past were nearly uniformly fatal, but more recently have been successfully treated with newer antifungal agents (such as voriconazole) and neurosurgical resection [104].

Infections due to a number of other fungi occur in solid-organ transplant recipients, including *Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum*, and *Zygomycetes*, *Mucor*, and *Rhizopus* spp. Infections caused by those fungi occur in specific settings and present as specific syndromes that should be considered by the clinician caring for immunosuppressed patients.

Cryptococcus neoformans is the second leading cause of invasive fungal infections in liver transplant recipients. This pathogen may cause pneumonia or meningitis, and patients with pulmonary disease often have CNS involvement as well. It is recommended that immunocompromised patients with cryptococcal infection should undergo lumbar puncture even if asymptomatic neurologically. Skin nodules are occasionally seen. The diagnosis is confirmed by India-ink staining and by testing for cryptococcal antigen in cerebrospinal fluid or sputum. Treatment consists of amphotericin B followed by oral fluconazole [105].

Coccidioides immitis is endemic in the southwestern United States and in Mexico. Between 7% and 9% of solid-organ transplant recipients residing in that area develop coccidioidomycosis, with an associated mortality rate of 25% in pulmonary cases and of up to 70% in disseminated cases [80]. The presentation of disease is variable, as multiple organ systems may be involved. The diagnosis must be made by microscopy, antigen detection, or tissue culture. Lifelong fluconazole prophylaxis for solid-organ transplant recipients who reside in endemic areas is advocated in some centers, though long-term outcome data are lacking. A reduction of calcineurin inhibitor dosage can be an adjunct benefit. The treatment is prolonged amphotericin B administration or azole therapy [106].

Histoplasmosis and blastomycosis infections occur in endemic areas of the American Midwest and in the Mississippi and Ohio River valleys. Invasive disease, either reactivation of latent fungi or a new infection, occurs in up to 2% of solid-organ transplant recipients, with the highest incidence in those areas. Invasive disease spreads from the lungs to the skin and bone marrow. Biopsy and samples for culture analysis may be obtained from skin lesions or from a bone-marrow aspirate. Amphotericin B or itraconazole are appropriate therapeutic agents [79].

Mucor and *Rhizopus* spp in the *Zygomycetes* class are soil fungi that, when inhaled, may cause a highly morbid, invasive rhinocerebral infection in profoundly immunosuppressed patients and in diabetic patients with poor glycemic control [107]. The diagnosis is established by biopsy; treatment is surgical debridement with adjuvant antifungal therapy (amphotericin B with the occasional addition of 5-flucytosine, itraconazole, or rifampin). The mortality rate associated with those types of infections is in excess of 50%.

Pneumocystis jiroveci pneumonia (PCP) is a common cause of pneumonia in immunosuppressed patients. PCP is associated with profound defects in cellular immunity and normally is seen with CD4-positive T-cell counts lower than 200 per μL [108]. Those indices are often seen with OKT3 therapy for AR. Prophylaxis with TMP-SMX or atovaquone (if sulfa allergic) makes PCP a rare entity; however, transplant recipients who have a respiratory illness but did not receive prophylaxis (e.g., because of allergy or noncompliance) should be evaluated promptly for PCP. Untreated PCP has a very high mortality rate. The diagnosis is typically established by bronchoscopy and BAL, with methenamine silver staining of washings, or by transbronchial biopsy. Normal findings should not delay further evaluation and therapy (the characteristic alveolar and interstitial changes seen on a chest radiograph are late findings). Even before the diagnosis of PCP is established, empiric therapy is normally started with intravenous TMP-SMX or inhaled pentamidine. Dapsone is used in patients with a sulfa sensitivity. Concurrent CMV infection is common, so CMV diagnostic studies should be undertaken in patients whose PCP fails to respond promptly to appropriate therapy.

Viral Infections

Viral infections have increasingly been recognized as important causes of morbidity and mortality in solid-organ transplant recipients. Viruses that are endemic and of little clinical concern in the general patient population may produce overwhelming infections in the host with suppressed cellular immunity. The recent appreciation of the immunomodulatory effect of several opportunistic viral pathogens gives even more reason for continued development of effective prophylaxis, diagnosis, and treatment modalities for this class of infectious agents. Immunosuppressed transplant recipients may develop serious viral infections by reactivation of latent virus, by transmission of the virus via the donor graft or via blood transfusion, or by exposure to the virus in the environment.

Pathogens known as the HHVs are important in the solid-organ transplant population (Table 186.4). Those viruses commonly cause disease during periods of intense immunosuppression, particularly early posttransplant and after antirejection therapy. They include many of the most important viral pathogens facing immunosuppressed patients, including CMV, EBV, the herpes simplex viruses (HSVs), and the varicella zoster virus (VZV).

CMV infections affect 30% to 75% of solid-organ transplant recipients, primarily within 2 weeks to 3 months posttransplant. The highest risk for CMV infections is in a CMV-seronegative recipient receiving a graft from a CMV-seropositive donor (the D+/R− graft) [109]. Lung and heart–lung transplant recipients have the highest rate of CMV disease (50% to 80%). Pancreas and pancreas–kidney transplant recipients have a rate of 50%; kidney, heart, or liver transplant recipients, 8% to 35% [110].

The most severe CMV disease is a primary infection in the D+/R− population. A superinfection (due to concurrent reactivation of an endogenous strain and transmission of a serotypically distinct strain of CMV) is typically intermediate in severity, whereas reactivation of latent disease is most often comparatively mild [111]. The range of clinical disease is vast: from asymptomatic infections (detected solely by a change in anti-CMV titer or by shedding of virus or viral DNA in blood, urine, or sputum) to tissue-invasive disease (which may affect the lungs, liver, or intestine). A typical mild infection produces a mononucleosis-like syndrome, including fever, malaise, and

TABLE 186.4

HUMAN HERPES VIRUSES (HHVs)

Virus	Eponym	Clinical syndromes
HHV-1	Herpes simplex virus-1	Mucocutaneous disease Primarily oral–labial symptoms Ocular keratitis Herpes simplex virus encephalitis
HHV-2	Herpes simplex virus-2	Mucocutaneous disease Primarily genital symptoms Ocular keratitis
HHV-3	Varicella zoster virus	Chickenpox, shingles Pneumonitis, encephalitis
HHV-4	Epstein–Barr virus	Infectious mononucleosis Hepatitis, pneumonitis Posttransplant lymphoproliferative disease Burkitt lymphoma
HHV-5	Cytomegalovirus	Mononucleosis, pneumonitis Hepatitis, gastroenteritis, retinitis
HHV-6	Roseola (6B)	Childhood febrile exanthema Mononucleosis, encephalitis Pneumonitis, disseminated disease
HHV-7		No clear clinical entities
HHV-8	Kaposi agent	Cutaneous lymphomas

myalgias, often accompanied by leukopenia. More severe disease clinically manifests with differing signs and symptoms, depending on the site(s) of invasive infection. GI ulceration with occasional hemorrhage is seen in GI disease. CMV pneumonitis may produce respiratory insufficiency and failure. CMV hepatitis may lead to liver failure and to severe pancreatitis can occur. CMV retinitis may produce vision changes, leading to blindness.

Formerly, the presence of CMV was suspected in patients who developed a viral prodrome, with a fourfold increase in anti-CMV titer or by direct observation of CMV inclusion bodies in biopsy specimens. Retrospective confirmation was on the basis of culture analysis that took 2 to 3 weeks. Those inadequate diagnostic techniques have been supplanted by the rapid "shell-vial" culture, in which virus is grown in culture with fibroblasts and examined by immunofluorescence microscopy after incubation with anti-CMV immunofluorescence-linked monoclonal antibodies [112].

A rapid antigenemia assay is also available that measures the levels of the pp65 CMV antigen in sample fluid, but accurate results depend on a normal white blood cell count [113]. Most recently, the polymerase chain reaction has been used to measure viral copy number in peripheral leukocytes and, like the antigenemia assay, may permit very early diagnosis of subclinical CMV infections in at-risk patients [114]. Investigators differ in their preference between those two techniques [115], but both are clearly useful. Overall, the new techniques allow substantiation of CMV infections with greater than 90% to 95% sensitivity and specificity within 24 to 48 hours.

Given the high prevalence and significant morbidity of CMV disease, prophylaxis with ganciclovir, valacyclovir, or valganciclovir for 3 to 6 months posttransplant is common, particularly in high-risk patients. Additional prophylaxis routinely is begun with initiation of antirejection therapy. Several randomized clinical trials have shown ganciclovir prophylaxis to be superior to acyclovir prophylaxis in preventing both reactivation and primary CMV disease in solid-organ transplant recipients [116–119].

A second approach to this problem is the close monitoring of at-risk patients with protocol antigenemia or polymerase chain reaction assays followed by empiric (so-called preemptive) therapy with ganciclovir, if levels rise above a predetermined threshold. This approach, though somewhat more cumbersome, has led to reductions in the burden of CMV disease in liver transplant recipients [120]. Prophylaxis, surveillance with empiric therapy, or a combination of both based on calculated risk is currently practiced in most transplant centers. However, in kidney transplant recipients, surveillance monitoring with preemptive therapy has not been shown to be superior to treatment based on symptomatic disease [121], and, consequently, the main focus in this population is on prophylaxis. Ganciclovir prophylaxis is used for lung, heart–lung, and heart transplant recipients as well [122–124], but data on surveillance, preemptive therapy, and efficacy in such recipients are limited.

Traditionally, treatment of established CMV infections consists of intravenous ganciclovir, followed in most cases by oral ganciclovir. Oral valganciclovir alone can achieve similar clinical outcomes [125]. Anti-CMV immune globulin is available and is commonly added to ganciclovir for the treatment of serious, life-threatening invasive CMV infections, although studies of this agent have been limited to its use in prophylaxis and are equivocal in showing efficacy [126]. Foscarnet (trisodium phosphonoformate) is used in those rare instances where ganciclovir-resistant strains of CMV are isolated. The data that clearly establish the efficacy of foscarnet in treating CMV disease are limited to CMV retinitis; efficacy equivalent to ganciclovir was observed, but foscarnet was associated with a higher rate of adverse effects (e.g., nephrotoxicity) [127].

The HSVs (HSV-1 and HSV-2) commonly cause mucocutaneous disease of the oropharynx (HSV-1) and the genitalia (HSV-2). In profoundly immunosuppressed patients, they may cause disseminated disease, including hepatitis, encephalitis, and pneumonitis. Most such infections are thought to be reactivation of latent virus [128], and the highest risk is in lung and heart transplant recipients. The diagnosis is established by identification of the virus by immunofluorescent monoclonal antibody staining or by Tzanck smear. Culture and rising anti-HSV antibody titers provide evidence as well. Treatment consists of acyclovir; most epidermal lesions respond to oral therapy, but any evidence of disseminated disease requires high-dose intravenous acyclovir and minimization of immunosuppression.

Infections associated with EBV are commonly detectable in solid-organ transplant recipients. The most common manifestations include the typical mononucleosis-type syndrome, pneumonitis, and hepatitis [129]. The diagnosis of EBV infections is made by detection of heterophile immunoglobin M antibodies in serum or by following titers of antibodies to viral capsid antigen or to early antigens. Polymerase chain reaction is also used to monitor viral activity and response to therapy. Treatment consists of acyclovir (or ganciclovir, when a CMV infection is also suspected). Severe invasive disease mandates a reduction in immunosuppressive therapy. The most important aspect of EBV, however, is its association with posttransplant lymphoproliferative disorders (PTLDs) (vide infra).

VZV commonly emerges from latency in immunosuppressed transplant recipients and causes an episode of shingles [75]. More rarely, VZV may cause disseminated infections, such as pneumonitis and encephalitis. The highest risk of disseminated VZV disease is in pediatric transplant recipients who have not been exposed to VZV (e.g., chickenpox); this type of

primary infection is associated with a high mortality rate (11%) [130]. Fortunately, the introduction of the varicella vaccine has markedly reduced this type of disease; the vaccine is recommended pretransplant for all pediatric and nonimmunosuppressed transplant candidates [131]. VZV infections are treated with acyclovir; with severe disseminated disease, immunosuppression is reduced [132]. No evidence supports the efficacy of anti-VZV immune globulin for treating severe VZV disease in immunocompromised patients, though it may be considered in nonimmunocompromised individuals.

The role of HHV-6 as a cause of clinical disease is not yet clearly established in solid-organ transplant recipients. Considerable evidence, primarily in bone marrow and stem cell transplant recipients, points to an association between HHV-6 and CNS syndromes, pneumonitis, and a mononucleosis-like immunosuppressive syndrome that may predispose to other opportunistic infections [133]. An association between HHV-6 activation with severe CMV disease has been reported, but understanding causality in this context is difficult. Treatment of neurologic diseases related to HHV-6 includes ganciclovir and foscarnet, either alone or in combination [133]. HHV-7 is not yet clearly associated with clinical syndromes that pose major problems in solid-organ transplant recipients. HHV-8 is linked to the development of Kaposi sarcoma in transplant recipients (vide infra).

Viral hepatitis is a significant problem, particularly in liver transplant recipients, who may have developed end-stage liver disease as a result of HBV or HCV infections. Primary HBV or HCV infections may occur during the transplant operation itself, because of donor graft or blood transfusion transmission.

Would-be donors positive for hepatitis B surface antigen (HBsAg) and/or anti-hepatitis B core antibodies (HBcAbs) are often excluded from donating any organ or tissue [134]. Organs other than the liver have been transplanted from isolated HBcAb-positive donors, without evidence of transmission, but the risk for transmission is unknown [135]. HCV-positive donors are normally excluded from donating any organ [136], except to status-1 patients whose death is imminent or to patients who already have such infections. Liver transplant candidates with HBV or HCV disease are transplanted; currently, their graft and patient survival rates, particularly in the short term, are comparable to those for recipients without HBV or HCV disease. At one time, HBV disease was a contraindication to a liver transplant; however, the use of lamivudine and HBV-immune globulin (HBIG) has significantly reduced the burden of recurrent HBV disease [137,138] and has allowed hundreds of patients with end-stage liver disease secondary to HBV to undergo successful transplants. The optimal duration of HBIG treatment is debatable.

However, the development of recurrent viral disease in patients with HCV is inevitable and may be clinically significant, depending on the severity of the disease [139]. Up to 25% of transplant recipients accelerate to cirrhosis within 5 to 10 years posttransplant, likely related to immunosuppressive therapy and rejection [140]. The care of transplant candidates with HCV includes extending the donor pool, tailoring antiviral treatment pre- and posttransplant, and offering a living donor transplant [141]. The idea of neutralizing human monoclonal antibodies against HCV is currently under clinical investigation [142].

As discussed previously, many of the HSVs are associated with invasive hepatitis, which may progress to fulminant disease. Hepatitis may also be caused by adenovirus infections in solid-organ transplant recipients. Several other viruses cause significant morbidity and mortality in this patient population. Adenoviral infections, though more common in hematopoietic cell transplant patients, do occur in solid-organ transplant recipients. Invasive adenoviral infections most commonly manifest as pneumonitis or hepatitis, both of which carry a poor prognosis [143].

Primary infections with HIV via an organ transplant from an HIV-positive donor have been described; HIV-positive status is ordinarily a contraindication to either donating or undergoing a transplant [144]. However, solid-organ transplant recipients infected with HIV have been identified and have enjoyed long-term survival posttransplant [145], given the success of long-term multidrug therapy for HIV. With the introduction of highly active antiretroviral therapy (HAART), the transplant community has now recognized HIV infections as a chronic condition. In fact, end organ failure develops in HIV-positive individuals as they age and/or from the side effects of their antiviral treatments. Short-term outcomes in HIV-positive transplant recipients have been promising [146]: the HIV load remains suppressed, CD4-positive T-lymphocyte counts are stable, and the risk of opportunistic infection is acceptable. However, major challenges in the care of HIV-positive transplant recipients include high graft rejection rates and multiple drug interactions between HAART and maintenance immunosuppression [147].

The polyomavirus, including BK, JC, and SV40, is a ubiquitous pathogen that has no clinical significance in immunocompetent hosts. BK virus (BKV) is tropic-specific for human transitional and renal tubular epithelial cells. After primary infection, which often occurs in early life, BKV establishes lifelong latency in the host's renal cells. Reactivation takes place when the host's immune system is weakened, such as during pregnancy or posttransplant immunosuppression. The diagnosis is made by detecting free viral particles in the urine, blood, or intranuclear viral inclusion-bearing cells (decoy cells) in urine cytology specimens. BKV nephropathy (BKN) has been increasingly recognized as an important entity in kidney transplant recipients since the mid-1990s; currently, it is seen in 1% to 9% of them within the first year posttransplant [148]. In advanced BKN, the graft failure rate has been reported as high as 60% [149]. Depending on the severity of renal tubule injury, clinical presentations of BKN can include fatigue, fever, mild hydronephrosis, or marked graft dysfunction. In bone marrow transplant recipients, hemorrhagic cystitis has been described. The diagnosis of BKV reactivation is made by urinary cytology, quantitative PCR analysis to measure the viral load in urine or plasma, and kidney biopsy [150]. The mainstays of caring for patients with BKN are to reduce immunosuppression and to closely monitor disease progression. Given the lack of specific antiviral agents against BKV, low-dose cidofovir or leflunomide has been used, with some success, in patients with persistent BKN [151,152].

Human papilloma viruses may cause disease through the development of tissue-specific growth leading to benign or malignant processes, including cervical cancer, cancer of the vulva and perineum, condyloma acuminatum, laryngeal polyposis, and nonmelanotic skin cancer (vide infra). Respiratory syncytial virus may produce a fulminant pneumonia in both adult and pediatric transplant recipients. The diagnosis is made by nasopharyngeal washing. More severe cases should be treated with ribavirin.

Parasitic Infections

Several common parasitic infections are seen in immunosuppressed solid-organ transplant recipients. *Toxoplasma gondii* presents as a brain abscess with neurologic changes [153]. It is seen late posttransplant, whereas a brain abscess in the early posttransplant period is more likely to be fungal [154]. Heart transplant recipients seem to be at greatest risk, possibly due to the presence of *T. gondii* cysts in donor myocardial tissue. If the heart donor was seropositive for *T. gondii*, the recipient

normally undergoes prophylactic treatment with pyrimethamine and sulfadiazine for 3 to 6 months posttransplant. Treatment of *T. gondii* infections consists of pyrimethamine and sulfadiazine; the mortality rate is high in transplant recipients who exhibit CNS disease.

MALIGNANCY

Solid-organ transplant recipients have a markedly increased risk of developing malignancy posttransplant. An extensive data collection tracks the epidemiology of tumors in transplant recipients; it was initiated and is maintained by the Israel Penn International Transplant Tumor Registry [155]. The increased incidence of malignancy is multifactorial, probably due to a combination of the activation of latent viruses with oncogenic potential, the direct oncogenic effect of immunosuppressive drugs such as cyclosporine, and, perhaps, environmental factors. Strong but indirect evidence points to the loss of immunologic surveillance as a mechanism of increased oncogenesis. The most common neoplasms in solid-organ transplant recipients are skin cancers, PTLD, lung cancer, Kaposi sarcoma, and carcinoma of the cervix. Of those neoplasms, lung cancer appears to occur at the same frequency as in the general population; the other neoplasms occur at increased frequency in solid-organ transplant recipients. PTLD presents the greatest challenge in terms of attendant high morbidity and mortality rates.

Posttransplant Lymphoproliferative Disorder

The term *PTLD* encompasses a very broad range of pathologies, from simple lymphoid hyperplasia to very aggressive monoclonal B-cell lymphomas. EBV infections play a central causative role. In particular, primary EBV infections posttransplant (EBV D+/R− match) and immunosuppression markedly increase the risk of PTLD [156]. Other risk factors include active CMV disease [157], CMV D+/R− match [158], increasing intensity of immunosuppression [159,160], and, possibly, HCV infections [161] and recipient cytokine gene polymorphisms [162].

PTLD is least common in adult kidney transplant recipients and most common in pediatric small-bowel transplant recipients. It is most common early posttransplant, concurrent with the most intense immunosuppression and with the use of anti–T-cell therapy for AR, particularly repeated courses. However, a subset of PTLD occurs late (several years) posttransplant. These late-occurring neoplasms appear to be related more to patient age, duration, and intensity of immunosuppression, and type of graft than to the more typical risk factors seen in early onset disease.

The clinical presentation of PTLD varies widely, as might be expected from the wide range of pathology encountered with this entity. Many patients experience fever, sweats, and myalgias as the only symptoms. Weight loss, diarrhea, and upper respiratory infection symptoms also are common; some, but not all, patients have lymphadenopathy. CNS involvement, which occurs in up to 20% of patients [163], often manifests as mental status changes. GI disease may be silent or may present as abdominal pain, GI bleeding, perforation with peritonitis, or bowel obstruction. Intrathoracic PTLD has a characteristic radiographic appearance of multiple circumscribed pulmonary nodules, which may or may not be accompanied by mediastinal lymphadenopathy. PTLD in the graft itself can present very similarly to AR; because the therapeutic approach to those two entities is diametrically opposed, a correct diagnosis on biopsy is essential.

Biopsy of suspected lesions is the gold standard in establishing the diagnosis of PTLD. Biopsy specimens are histologically graded (based on cell morphology and nodal architecture) and assessed for clonality (polyclonal or monoclonal) and for the presence of an EBV genome and copy number. Specific cell marker studies are required to establish the cell of origin, but most lesions are EBV positive and of B-cell lineage. Pathologists familiar with PTLD as well as with graft rejection and opportunistic infections should review the biopsy results. Consensus conference standards for the grading and classification of PTLD are used [164]. Histologic classification currently uses the Harris standard formulation [165]. EBV serology does not typically add to the diagnostic workup of PTLD, with many false-negatives in patients with established primary EBV infections [166,167]. Similarly, peripheral cytology is not helpful in making the diagnosis [168]. If PTLD is suspected, patients should undergo imaging of the head, thorax, and abdomen. Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT scanning has been increasingly used as a diagnostic and/or staging tool and in follow-up studies of PTLD patients [169].

Currently, there is little information to provide direction regarding optimal prophylaxis against PTLD. Clearly, it is important to identify, and closely monitor, high-risk patients (e.g., children; liver and small-bowel transplant recipients; EBV-negative transplant recipients, particularly those with an EBV-positive donor; and transplant recipients on intense antilymphocyte therapy for rejection). Similarly, OKT3 therapy should not be used in high-risk patients without a definitive diagnosis of AR on biopsy. Both antiviral agents and passive immune transfer with anti-EBV immune globulin have been proposed as prophylaxis against PTLD, but data supporting those approaches are lacking. Several trials are ongoing to establish the best prophylactic approach [170]. Intriguingly, the improvements in baseline immunosuppression preventing AR appear to decrease the frequency of PTLD, likely as a byproduct of reducing the frequency of antilymphocyte antibody therapy [171].

Treatment of established PTLD depends on each patient's clinical situation and histologic diagnosis. With few trials to guide therapy, a graded, individualized approach is taken. Ordinarily, immunosuppression is reduced to minimal levels, and specific therapy is directed at the neoplasm. In 25% to 50% of patients, PTLD regresses after their immunosuppression is reduced [172].

Surgical intervention is clearly indicated for patients with GI PTLD that manifests as aggressive disease (e.g., viscus obstruction or perforation). Surgical debulking of the tumor burden has also been used in amenable cases [173], as has radiotherapy [174]. Isolated CNS disease initially should be treated with external beam irradiation.

Medical approaches to treating PTLD include (a) antiviral medications (e.g., acyclovir, ganciclovir) [175]; (b) interferon-α2b [176]; (c) immunoglobulins [75,175]; (d) standard, low-dose, and high-dose chemotherapy protocols [177,178]; and (e) most recently, monoclonal antibodies directed against B-cell surface markers, such as CD19 and CD20 (rituximab) [179]. In unusual cases, immunomodulatory therapy with adoptive transfer of cytotoxic T cells sensitized to EBV has been attempted with some success [180].

Late-onset PTLD, occurring more than 1 to 2 years posttransplant, often does not respond to the reduction in immunosuppression and to the medical therapy typically used in patients with early-onset disease. Often EBV-negative, late-onset PTLD is difficult to treat because of side effects, including infectious complications of the aggressive chemotherapy that is often required. Similarly, CNS involvement may be a marker for PTLD that is potentially refractory to therapy, possibly because of the relatively privileged immune site. Treatment options include intrathecal administration of interferon-α and anti–B-cell

antibody therapy along with local radiotherapy, but the prognosis remains guarded [163,181].

Skin Cancer

The most common neoplasms associated with transplants and immunosuppression are nonmelanotic skin cancers. These lesions increase in frequency with sunlight exposure and with increasing time posttransplant. Often-quoted studies show a prevalence of 66% in transplant recipients in Australia after 24 years of surveillance [182] and 40% after 20 years in the Netherlands [183]. Those figures correlate to a 4- to 21-fold increase in prevalence in transplant recipients, as compared with the immunocompetent population, with synergistic increases seen in the areas of highest sunlight exposure.

Most skin cancers in transplant recipients are squamous cell carcinomas. Many recipients develop multiple lesions, and the age at onset is markedly lower than in the general population. The incidence of melanomas is also higher representing 4.8% of skin cancers in kidney transplant recipients, as compared with 2.7% in the general population [155]. Even nonmelanotic squamous cell carcinomas behave more aggressively in transplant recipients, with lymph node metastasis and a 6% mortality rate due to disseminated disease [184]. On identification of skin lesions, prompt surgical extirpation should be undertaken. Solid-organ transplant recipients are instructed to avoid direct exposure to sunlight for any prolonged period and to liberally use sunblock. Clearly, close dermatologic counseling and follow-up are warranted in this patient population.

Kaposi Sarcoma

Kaposi's sarcoma (KS) is a multicentric, vascularized, nodular neoplasm that may affect the skin, visceral tissues (such as the lungs and GI tract), or both. Endemic in the Mediterranean region and Middle East, it is strongly associated with either endogenous or exogenous immunosuppression, as a result both of AIDS and of immunosuppressive therapy. The incidence of this disease in U.S. transplant recipients is 0.4%, which represents a 20-fold increase over the basal rate in the population at large [155]. That figure rises to 1.6% in Italian kidney-transplant recipients and up to 4.0% in Saudi Arabian transplant recipients [185,186]. Recently, human herpes virus (HHV)-8 has been implicated as a causal agent in KS. One small series showed HHV-8 seropositivity pretransplant to be a relative risk factor for development of KS posttransplant [187].

Cutaneous KS is readily identified by clinical appearance and biopsy. But patients with only visceral KS often present with more advanced disease, usually GI bleeding or viscus perforation, sometimes dyspnea related to pulmonary disease. Immunosuppression should be reduced to the extent possible, after which about 30% to 55% of patients will experience remission. Chemotherapy is reserved for patients with visceral KS and for those who do not experience remission after their immunosuppression is reduced. However, of patients with visceral KS, 45% to 50% die of it. Viral studies and antiviral therapy do not yet have any well-established role in fighting this neoplasm, but anecdotal evidence indicates that certain patients may respond to antiviral agents (e.g., ganciclovir).

Cervical Cancer

The rate of development of cervical intraepithelial neoplasia is elevated by 10- to 14-fold in solid-organ transplant recipients and may approach 50% [188,189]. Cervical carcinoma was seen in 10% of all women with posttransplant cancer in the Transplant Tumor Registry [155]. Close surveillance by pelvic examination and Papanicolaou smear is essential in this population, given the increased incidence of disease. In transplant recipients with more advanced cervical cancer, a functioning graft poses complications in selecting and carrying out appropriate therapy. Limited data are available to guide therapy.

Transmitted and Recurrent Malignancy

Case reports have described patients who received grafts that harbored malignant cells, leading to the development of malignancy. Transmission to transplant recipients of renal cell carcinoma, metastatic cancer of the breast or lung, and melanoma has been reported. Currently, cancer or recent history of cancer is a contraindication to organ donation, with the possible exception of some low-grade skin cancers, noninvasive CNS neoplasms, and small, limited, extirpated cancers that are not likely to recur or spread. Nonetheless, some grafts are found to contain foci of neoplasia, which develop into a clinically significant cancer in recipients. This finding emphasizes the need for a thorough examination of donors during organ procurement, particularly considering the present trend toward the use of older donors.

Patients with a history of malignancy clearly are at risk for recurrent disease posttransplant, presumably due to the use of immunosuppression. Data from the Transplant Tumor Registry show a 21% recurrence rate, with the highest rates seen in patients with multiple myeloma (67%), nonmelanotic skin cancer (53%), bladder cancer (29%), soft-tissue sarcoma (29%), renal cell cancer (27%), and breast cancer (23%) [190]. Tumors were least likely to recur if more than 5 years had passed between cancer treatment and the transplant.

Liver transplants to treat patients with primary, well-circumscribed liver tumors represent a special case. In this population, liver tumor size and the number of liver tumors are considered indicative of the likelihood of disease recurrence and patient survival posttransplant [191,192]. Adjuvant techniques, such as cryoablation and radiofrequency ablation, to reduce the tumor burden pretransplant have been used, but currently the data are insufficient to clearly define the ability of adjuvant techniques to reduce posttransplant morbidity and mortality secondary to disease recurrence. Risk factors for recurrence include tumor size > 6 cm, number of nodules > 5, and vascular invasion per the final pathology report [193]. Clearly, tumor biology dictates the risk of disease recurrence and needs to be further characterized, representing an interesting, perhaps promising experimental arena.

SUMMARY

Over the past several decades, advances in the field of solid-organ transplantation have been significant, such that the primary limitation to further expansion may be considered to be logistic, related to organ availability. Dramatic improvements in medical care and technology have broadened the pool of potential recipients to include those who would have been considered too sick, with too much comorbidity, even a few years ago. Until medical science is able to develop immunosuppression without side effects, the predominant challenges in transplantation will remain the prevention, detection, and treatment of rejection; the prophylaxis, diagnosis, and treatment of infections; and the prevention, detection, and treatment of malignancy. Those clinical problems have only grown in the nearly six decades since the first successful kidney transplant was performed, and they promise to become even more complex throughout the twenty-first century.

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CHAPTER 187 ■ CRITICAL CARE OF THE LIVER AND INTESTINAL TRANSPLANT RECIPIENTS

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INTRODUCTION

The field of liver transplantation has undergone remarkable advances in the last two decades. From an essentially experimental procedure with poor results in the early 1980s, it has progressed to become the accepted treatment of choice for patients with acute and chronic end-stage liver disease. One-year survival rates have increased from 30% in the early 1980s, to more than 85% at present. The major reasons for this dramatic improvement in outcome include improved surgical and preservation techniques, better immunosuppressive regimens, more effective treatment of rejection and infection, and improved care during the critical perioperative period. The field of intestinal transplantation has also made tremendous strides in the last 20 years, though perhaps has not enjoyed the degree of success seen with liver transplantation. Nonetheless, results continue to improve and it is approaching success rates that are not dramatically inferior compared with liver transplantation.

Despite the improved results, both liver and intestinal transplantation remain major undertakings, with potential for complications affecting every major organ system. This chapter focuses on the critical care of these challenging and complicated patients, including preoperative selection and evaluation, intraoperative care, postoperative care, and management of potential complications.

LIVER TRANSPLANTATION

History

The origins of modern clinical liver transplantation date back to the late 1950s, when the surgical techniques were perfected in the dog model [1]. The first human liver transplant was performed by Starzl in 1963 [2], but not until 1967 was the first successful such transplant performed [3]. Little progress was made in the field over the next decade. It remained a dangerous procedure, reserved for terminal patients.

In the early 1980s, liver transplantation proliferated for a variety of reasons, the most important being the introduction of cyclosporine [4]. At that time, it was the most specific immunosuppressive agent and allowed for a dramatic rise in all organ transplants. Patient survival rates for liver recipients on cyclosporine more than doubled. In the late 1980s, the introduction of University of Wisconsin (UW) preservation solution extended the cold preservation time of the cadaver liver from 8 to 24 hours [5].

As the success of liver transplantation grew, so did the indications and the number of people awaiting a transplant. With each passing year, there was an ever increasing disparity between the number of transplants performed and the number of patients awaiting transplant. In 1988, there were approximately 1,500 transplants performed and 3,000 patients awaiting a transplant. In 2008, according to the UNOS Database, 6,319 liver transplants were performed in the United States, while 16,584 patients were listed waiting for an available/suitable organ (UNOS/OPTN, www.optn.transplant.hrsa.gov/, accessed August, 2009) [6].

Given this increasing disparity between the number of actual and potential recipients, recent attempts have been made to expand the donor pool. Some of this increase in donors has been achieved by the use of livers that are considered marginal and would not have been used for transplant a decade ago. Recently, the use of organs from donors after cardiac death (also referred as nonheart beating donors) has emerged as an important source of organs in response to the significant growth of the waiting list. Donation after cardiac death (DCD) involves those donors who present a severe neurological injury and/or irreversible brain damage but still have minimal brain function. In 2000, only 11 centers used DCD livers, increasing to 62 centers in 2007 [7–9].

Innovative surgical procedures have also been used in order to increase the donor pool. These procedures include, but are not limited to, living donor liver transplantation, split-liver transplantation, and dual liver transplantation. Living donor transplants involve transplanting a lobe or part of a lobe from a healthy donor into a potential recipient. Split-liver transplantation involves dividing a cadaver liver into two functional grafts, which can be transplanted into two recipients. Dual liver transplantation involves the use of two lobes (usually two left lobes) from two living donors that are implanted into one adult recipient. These procedures are helping expand the donor pool, but are also associated with unique problems.

Proper allocation of the scarce resource of a deceased donor liver graft has always been an important issue in the development of the field. Recent effects have focused on directing organs to individuals with the greatest need, rather than those with the longest waiting time. In the United States, this lead to the development and adaptation in 2002 of the MELD (Model for End-Stage Liver Disease) and PELD (Pediatric End-Stage Liver Disease) scoring systems [10].

Preoperative Evaluation

A liver transplant is indicated for liver failure, whether acute or chronic. Liver failure is signaled by a number of clinical symptoms (e.g., ascites, variceal bleeding, hepatic encephalopathy, malnutrition) and by biochemical liver test results that suggest impaired hepatic synthetic function (e.g., hypoalbuminemia, hyperbilirubinemia, coagulopathy). The cause of liver failure often influences its presentation. For example, patients with acute liver failure generally have hepatic encephalopathy and coagulopathy, whereas patients with chronic liver disease most commonly have ascites, gastrointestinal (GI) bleeding, and malnutrition.

A host of diseases are potentially treatable by a liver transplant. Broadly, they can be categorized as acute or chronic, and then subdivided by the cause of the liver disease (Table 187.1). Chronic liver diseases account for the majority of liver transplants today. The most common cause in North America is chronic hepatitis, usually due to hepatitis C, less commonly to hepatitis B. Chronic alcohol abuse accelerates the process, especially with hepatitis C. Progression from chronic infection to cirrhosis is generally slow, usually 10 to 20 years. Chronic hepatitis may also result from autoimmune causes, primarily in women; it can present either acutely over months or insidiously over years [11]. Alcohol often plays a role in end-stage liver disease (ESLD) secondary to hepatitis C, but it may also lead to liver failure in the absence of that viral infection. In fact, alcohol is the most common cause of ESLD in the United States. Such patients are generally suitable candidates for a transplant as long as an adequate period of sobriety can be documented. Most of the centers in the United States require a minimum of 6 months of demonstrated abstinence and an adequate evaluation and treatment period for alcohol addiction. In spite of this strict pretransplant screening the rate of alcohol use after transplant can reach 42% in the first 5 years after transplant [12]

TABLE 187.1

DISEASES POTENTIALLY TREATABLE BY A LIVER TRANSPLANT

Cholestatic liver diseases
Primary biliary cirrhosis
Primary sclerosing cholangitis
Biliary atresia
Alagille's syndrome
Chronic hepatitis
Hepatitis B
Hepatitis C
Autoimmune hepatitis
Alcohol liver disease
Metabolic diseases
Hemochromatosis
Wilson's disease
α_1-Antitrypsin deficiency
Tyrosinemia
Cystic fibrosis
Hepatic malignancy
Hepatocellular carcinoma
Neuroendocrine tumor metastatic to liver
Fulminant hepatic failure
Others
Cryptogenic cirrhosis
Polycystic liver disease
Budd–Chiari syndrome
Amyloidosis

Cholestatic disorders also account for a significant percentage of transplant candidates with chronic liver disease. In adults, the most common causes are primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). PBC, a destructive disorder of interlobular bile ducts, can progress to cirrhosis and liver failure over several decades. It most commonly affects middle-aged women. PSC, a disease characterized by inflammatory injury of the bile duct, occurs mostly in young men, 70% of whom have inflammatory bowel disease [13]. In children, biliary atresia is the most common cholestatic disorder. It is a destructive, inflammatory condition of the bile ducts; if untreated, it usually results in death within the first 1 to 2 years of life.

A variety of metabolic diseases can result in progressive, chronic liver injury and cirrhosis, including hereditary hemochromatosis (an autosomal recessive disorder characterized by chronic iron accumulation, which may result in cirrhosis, cardiomyopathy, and endocrine disorders including diabetes), α_1-antitrypsin deficiency (which may result in cirrhosis at any age, most commonly in the first or second decade of life), and Wilson's disease (an autosomal recessive disorder of

copper excretion, which may present as either fulminant hepatic failure or chronic hepatitis and cirrhosis) [14].

Hepatocellular carcinoma (HCC) may be a complication of cirrhosis from any cause, most commonly with hepatitis B, hepatitis C, hemochromatosis, and tyrosinemia. In 2007, almost 15% of all liver transplants in the United States were performed in patients with a diagnosis of HCC. HCC patients may have stable liver disease, but are not candidates for hepatic resection because of the underlying cirrhosis; they are best treated with a liver transplant. The best transplant candidates are those with a single lesion less than 5 cm in size or with no more than three lesions, the largest no greater than 3 cm in size (known as the Milan criteria). Transplantation outside of these criteria is usually associated with higher recurrence rates, though some centers have shown acceptable 5-year survival in patients that have tumors that slightly exceed the Milan criteria [15,16].

Currently, in the United States, only the patients within Milan criteria are eligible for priority listing for liver transplantation. The amount of waiting list time for patients with HCC remains a critical factor in the success of liver transplantation, as long waiting times may lead to disease progression. Recently downstaging treatment, with transarterial chemoembolization and radiofrequency ablation, has emerged as a possible option for those patients who slightly exceed Milan criteria [17].

A host of other diseases may lead to chronic liver failure and are potentially amenable to treatment with a transplant, including Budd–Chiari (obstruction of the hepatic veins secondary to thrombus, which leads to hepatic congestion, ascites, and eventually liver damage) and polycystic liver disease (in which a large number of cysts, depending on their size, can lead to debilitating symptoms).

Acute liver disease, more commonly termed fulminant hepatic failure (FHF), is defined as the development of hepatic encephalopathy and profound coagulopathy shortly after the onset of symptoms, such as jaundice, in patients without preexisting liver disease. The most common causes in the Western world include acetaminophen overdose, acute viral hepatitis, various drugs and hepatotoxins, and Wilson's disease; often, however, no cause is identified [18]. Treatment consists of appropriate critical care support, giving patients time for spontaneous recovery. The prognosis for spontaneous recovery depends on the patient's age (those younger than 10 and older than 40 years have a poor prognosis), the underlying cause, and the severity of liver injury (as indicated by degree of hepatic encephalopathy, coagulopathy, and kidney dysfunction) (Table 187.2) [19,20]. A subset of patients may have delayed onset of hepatic decompensation that occurs 8 weeks to 6 months after the onset of symptoms. This condition is often referred to as subacute hepatic failure; these patients rarely recover without a transplant.

TABLE 187.2

ADVERSE PROGNOSTIC INDICATORS FOR PATIENTS WITH ACUTE LIVER FAILURE

(I) Acetaminophen toxicity
pH < 7.30
Prothrombin time > 100 sec (INR > 6.5)
Serum creatinine > 300 µmol/L (> 3.4 mg/dL)

(II) No acetaminophen toxicity
Prothrombin time > 100 sec (INR > 6.5)
Age < 10 or > 40 y
Non-A, non-B hepatitis
Duration of jaundice before onset of encephalopathy > 7 d
Serum creatinine > 300 µmol/L (> 3.4 mg/dL)

TABLE 187.3

INDICATIONS FOR A LIVER TRANSPLANT EVALUATION IN PATIENTS WITH CHRONIC LIVER DISEASE

Clinical indications
- Refractory ascites
- Spontaneous bacterial peritonitis
- Recurrent or severe hepatic encephalopathy
- Hepatorenal syndrome
- Significant weakness, fatigue, or progressive malnutrition
- Recurrent cholangitis or severe pruritus
- Progressive bone disease

Biochemical indications
- Serum albumin < 3.0 g/dL
- Serum INR > 1.7
- Serum bilirubin > 2 mg/dL (> 4 mg/dL for cholestatic disorders)

Indications for Transplant

Chronic Liver Disease. The simple presence of chronic liver disease with established cirrhosis is not an indication for a transplant (Table 187.3). Some patients have very well-compensated cirrhosis with a low expectant mortality. Patients with decompensated cirrhosis, however, have a poor prognosis without transplant. The signs and symptoms of decompensated cirrhosis include the following:

1. *Hepatic Encephalopathy (HE):* In its early stages, HE may begin with subtle sleep disturbances, depression, and emotional liability. Increasing severity of HE is indicated by increasing somnolence, altered speech, and at the extreme end, coma. Evaluation of the severity of HE is based on the West Haven criteria of altered mental status. A common finding on physical examination is asterixis, an ability to maintain position, which is most commonly tested by having the patients outstretch their arms and hold them in dorsiflexion. However, other simple tests (such as tongue protrusion, dorsiflexion of the foot, or asking the patient to grasp the examiner's fingers) can also trigger the asterixis. Blood tests often reveal an elevated serum ammonia level. HE may occur spontaneously, but is more commonly triggered by a precipitating factor such as infections, GI bleeding, use of sedatives, constipation, diuretics, electrolyte imbalance, or excessive dietary protein intake. The purpose of treatment is to correct the precipitating factor in combination with pharmacological management including nonabsolvable disaccharides (i.e., lactulose), and antibiotics such as neomycin, rifaximin, and metronidazole.
2. *Ascites:* Ascites is generally associated with portal hypertension. The initial approach to the management of ascites is sodium restriction and diuretics. If this approach is not successful, patients may require repeated large-volume (4 to 6 L) paracentesis. A better option to diuretic-resistant ascites requiring frequent paracentesis is transjugular intrahepatic portosystemic shunting (TIPS). A potential complication of TIPS is progression of liver failure or disabling encephalopathy. Patients with signs of far-advanced liver disease such as hyperbilirubinemia, HE, and renal dysfunction are generally not good candidates for TIPS.
3. *Spontaneous Bacterial Peritonitis (SBP):* This complication of chronic liver failure generally signals advanced disease. Anaerobic Gram-negative bacteria (*Escherichia coli, Klebsiella pneumoniae*) account for 60% of the cultured organisms; Gram-positive cocci account for the remainder. Diagnosis is confirmed if a tap of the abdominal fluid shows

a polymorphonuclear neutrophil (PMN) count of > 250 per mL. If a traumatic tap is performed (red cells > 10,000 per mL), the PMN count should be corrected, subtracting 1 PMN for every 250 red cells. Treatment is generally with a third-generation cephalosporin. The recurrence rate of SBP at 1 year is up to 70%; therefore, prophylaxis with antibiotics (norfloxacin or ciprofloxacin) is highly recommended. The long-term prognosis of patients who develop SBP is extremely poor with mortality rates of 50% to 70% at 1-year follow-up [21].

4. *Portal Hypertensive Bleeding:* The likelihood of patients with cirrhosis developing varices ranges from 35% to 80%. About one-third of those with varices will experience bleeding. The risk of recurrent bleeding approaches 70% by 2 years after the index bleeding episode. Each episode of bleeding is associated with a 30% mortality rate. Thus, urgent treatment of the acute episode and steps to prevent rebleeding are essential. Endoscopy is indicated to diagnose and treat the acute bleed with either band ligation or sclerotherapy. Other therapies include vasoactive drugs such as octreotide or vasopressin, balloon tamponade, TIPS, and emergency surgical procedures (such as a portosystemic shunt or transection of the esophagus). Generally, patients whose endoscopic procedure fails should undergo emergency TIPS, if feasible, to control bleeding. Beta-blockers have been shown to be of value in preventing the first bleeding episode in patients with varices and in preventing rebleeding.
5. *Hepatorenal Syndrome (HRS):* In patients with advanced liver disease and ascites, HRS is characterized by oliguria (< 500 mL of urine per day) in association with low urine sodium (< 10 mEq per L). It is a functional disorder; the kidneys have no structural abnormalities, and the urine sediment is normal. The differential diagnosis includes acute tubular necrosis, drug nephrotoxicity, and chronic intrinsic renal disease. HRS may be precipitated by volume depletion from diuresis, SBP, or agents such as nonsteroidal antiinflammatory drugs. Patients may require dialysis support, but the only effective treatment is a liver transplant.
6. *Others:* Other signs and symptoms of decompensated cirrhosis include severe weakness and fatigue, which may sometimes be the primary symptoms. Such weakness can be debilitating, leading to the inability to work or even to carry out day-to-day functions. It may be associated with malnutrition and muscle wasting, which at times may be quite severe. Biochemical abnormalities and loss of synthetic function in advanced ESLD are associated with a low-serum albumin, a high-serum bilirubin, and a rise in the serum international normalized ratio (INR).

The severity of illness and prognosis of patients with chronic liver disease can be estimated by a number of different scoring models including the Childs–Pugh–Turcotte score and the MELD score. The latter is now widely used in the United States for the allocation of organs. It is based on a predicted 3-month mortality for patients awaiting a liver transplant, and uses 3 laboratory values to generate a score which determines priority. The three laboratory values used are serum bilirubin, serum creatinine, and INR. The format is as follows:

$$\begin{aligned}\text{MELD Score} = {} & 0.957 \times \log_e(\text{creatinine mg per dL}) \\ & + 0.378 \times \log_e(\text{bilirubin mg per dL}) \\ & + 1.120 \times \log_e(\text{INR}) \\ & + 0.643\end{aligned}$$

For pediatric patients, the scoring system is somewhat different. The PELD (pediatric end-stage liver disease) score is calculated using the following factors: serum bilirubin, albumin, and INR, the age of the patient (additional points if < 1 year old), and if the patient has growth failure [22].

Acute Liver Disease. Patients with FHF should be considered for transplant if they have any one of a number of poor prognostic indicators that predict a low likelihood for spontaneous recovery of liver function (Table 187.2). Generally, FHF patients are more acutely ill than chronic liver failure patients, and thus require more intensive care pretransplant. FHF patients have more severe hepatic parenchymal dysfunction, as manifested by coagulopathy, hypoglycemia, and lactic acidosis. Infectious complications are more common, as is their incidence of kidney failure and neurologic complications, especially cerebral edema.

Coagulopathy is usually secondary to the impaired hepatic synthesis of clotting factors. A component of consumption, as a result of disseminated intravascular coagulation (DIC), may also be associated with FHF. Close attention should be given to the serum glucose level, which is more likely to be decreased in FHF patients. Intravenous (IV) glucose should be administered at a sufficient rate to maintain euglycemia.

The prevalence of bacterial infection in FHF patients is very high, a reflection of the loss of the liver's immunologic functions. The respiratory and urinary systems are the most common sources. In addition, almost one-third of FHF patients develop some form of fungal infection, usually secondary to *Candida* species [23]. Sepsis is generally a contraindication to a transplant; if it is unrecognized pretransplant, the outcome posttransplant is poor.

Multiple organ dysfunction syndrome, characterized by respiratory distress, kidney failure, increased cardiac output, and decreased systemic vascular resistance, is a well-described complication of FHF. It may be due to impaired clearance of vasoactive substances by the liver. Mechanical ventilation and dialysis support may become necessary pretransplant. Hemodynamic abnormalities may manifest as hypotension and worsening tissue oxygenation.

Cerebral edema is substantially more common in FHF patients. As many as 80% of patients dying secondary to FHF have evidence of cerebral edema. The pathogenesis is unclear, but it may be due to potential neurotoxins that are normally cleared by the liver. Diagnosis may be problematic; patients are often sedated and ventilated, making clinical examination difficult. Radiologic imaging is neither sensitive nor specific. Several centers have tried intracranial pressure (ICP) monitoring; therapy (e.g., mannitol, hyperventilation, thiopental) can then be directed to achieve an adequate cerebral perfusion pressure. ICP monitoring also helps predict the likelihood of neurologic recovery posttransplant. Sustained cerebral perfusion pressures of less than 40 mm Hg have been associated with postoperative neurologic death. Disadvantages of ICP monitoring include the risks of performing it in patients with severe coagulopathy; it is also a possible source of infection and may precipitate an intracranial hemorrhage.

Contraindications for Transplant

The indications for a liver transplant are numerous (and are increasing), but the numbers of absolute contraindications are few (and have decreased with time). There are no specific age limits for recipients; their mean age is steadily increasing. Patients must have adequate cardiac and pulmonary function. Other contraindications, as with other types of transplants, include uncontrolled systemic infection and malignancy. HCC patients with metastatic disease, obvious vascular invasion, or significant tumor burden are not good transplant candidates. Patients with other types of extrahepatic malignancy should be deferred for at least 2 years after completing curative therapy before a transplant is attempted.

Currently, the most common contraindication in the United States to a liver transplant is ongoing substance abuse. Before considering patients for a transplant, most centers require a documented period of abstinence, demonstration of compliant behavior, and willingness to pursue a chemical dependency program.

Unique to patients with chronic liver disease, a transplant may be contraindicated in the presence of severe hepatopulmonary syndrome or pulmonary hypertension. Hepatopulmonary syndrome is characterized by impaired gas exchange, resulting from intrapulmonary arteriovenous shunts. These shunts may lead to severe hypoxemia, especially when patients are in the upright position (orthodeoxia). A transplant may be contraindicated if intrapulmonary shunting is severe, as manifested by hypoxemia that is only partially improved with high inspired oxygen concentrations. Pulmonary hypertension (mean pulmonary artery pressure > 25 mm Hg in the setting of portal hypertension) is seen in a small proportion of patients with established cirrhosis. Its exact cause is unknown [24]. Diagnosing pulmonary hypertension pretransplant is critical, because major surgical procedures in the presence of nonreversible pulmonary hypertension are associated with a very high risk of mortality. The initial screening is usually performed with transthoracic Doppler echocardiography (TTE) which can estimate pulmonary arterial systolic pressure when tricuspid regurgitation is present. TTE presents a sensitivity of 97% and specificity of 77% in diagnosing pulmonary hypertension in the setting of liver failure. In patients with elevated pulmonary arterial systolic pressure (> 50 mm Hg), a more invasive assessment (right heart catheterization) is recommended. It has been shown that perioperative mortality is directly proportional to the mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance. For these reasons, most transplant centers consider a mPAP greater than 35 mm Hg to be an absolute contraindication for transplant. If the mPAP can be lowered below that value using medications (epoprostenol, sildenafil), the patient can still be considered for transplant [24].

Another absolute contraindication for liver transplantation, in case of acute liver failure, is a presence of unresponsive cerebral edema with sustained elevation of intracranial pressure (> 50 mm Hg) and a persistent decrease in cerebral perfusion pressure (< 40 mm Hg).

Intraoperative Care

A detailed description of the operative procedure and anesthetic management is beyond the scope of this chapter. A basic understanding of the intraoperative course is necessary, however, to aid in postoperative care and monitoring for possible complications.

The operation itself may be divided into three phases: preanhepatic, anhepatic, and postanhepatic. The preanhepatic phase involves mobilizing of the recipient's diseased liver in preparation for its removal. The basic steps include isolating the supra- and infrahepatic vena cava, portal vein, and hepatic artery, and then dividing the bile duct. Given existing coagulopathy and portal hypertension, the recipient hepatectomy may be the most difficult aspect of the procedure. The anesthesia team must be prepared to deal with excessive blood loss during this time.

Once the above-named structures have been isolated, vascular clamps are applied. The recipient's liver is removed, thus beginning the anhepatic phase. This phase is characterized by decreased venous return to the heart because of occlusion of the inferior vena cava and portal vein. Many centers routinely employ a venous bypass system during this time: blood is drawn from the lower body and bowels via a cannula in the common femoral vein and portal vein, and returned through a central venous cannula in the upper body. Potential advantages of bypass include improved hemodynamic stability, reduction of bleeding from an engorged portal system, and avoidance of elevated venous pressures in the renal veins. However, many centers do not routinely use venovenous bypass (VVB). Very few randomized trials have measured specific clinical outcomes with or without VVB. In one randomized trial, postoperative renal function and the need for hemodialysis or hemofiltration were no different between liver recipients with versus without VVB [25]. This, combined with the potential complications of VVB (air embolism, thromboembolism, hypothermia, hemodilution, cannula and incision-related morbidity, trauma to vessels, and incremental costs), have led some centers to adopt a selective use for VVB—reserving it for patients without portal hypertension or for those patients who demonstrate hemodynamic instability with a trial of caval clamping [26].

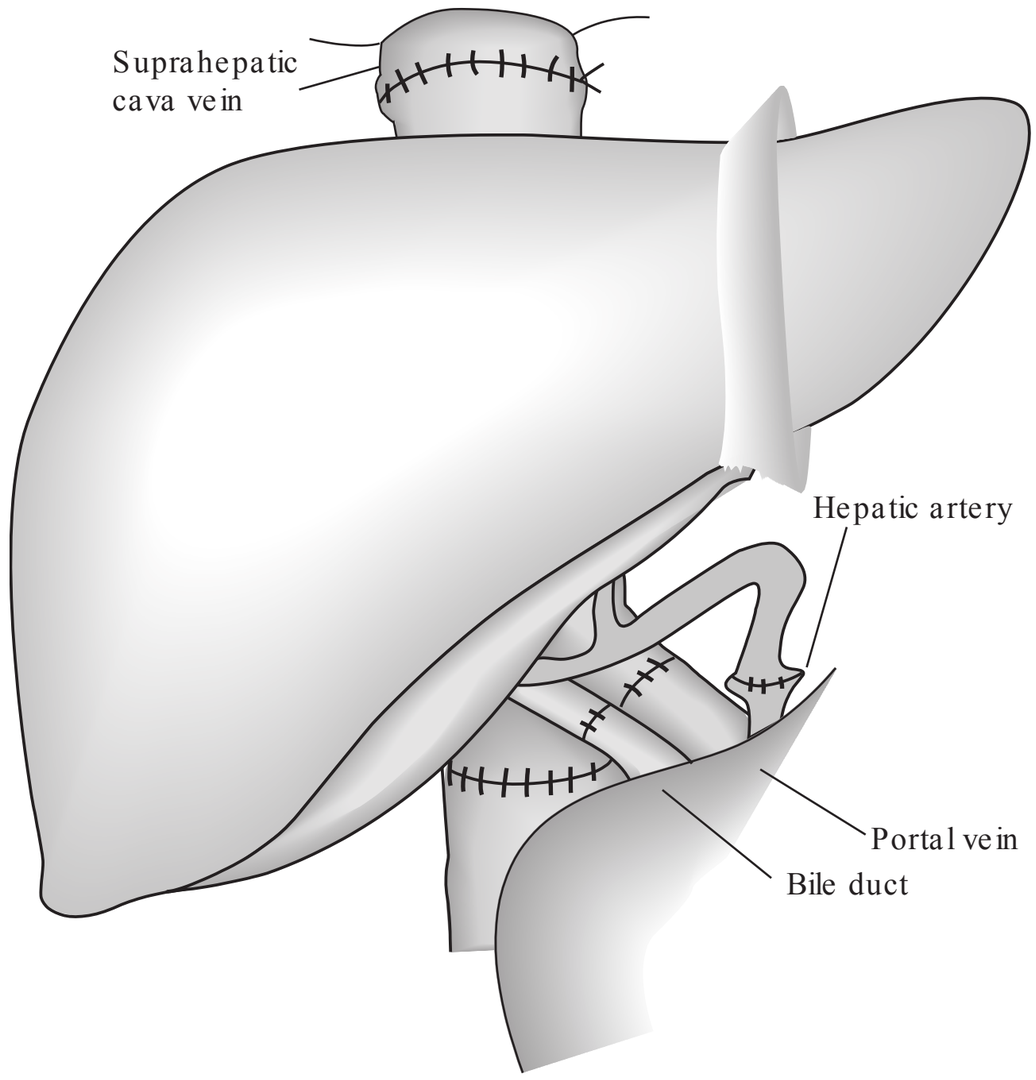

FIGURE 187.1. Illustration of standard liver transplant procedure with replacement of the recipient's inferior vena cava. Typical vascular and biliary anastomoses are shown.

With the recipient liver removed, the donor liver is anastomosed to the appropriate structures to place the new liver in an orthotopic position (Fig. 187.1). The suprahepatic caval anastomosis is performed first, followed by the infrahepatic cava and the portal vein. The portal and caval clamps may be removed at this time, allowing reperfusion of the new liver. Either before or after this step, the hepatic artery may be anastomosed.

With the clamps removed and the new organ reperfused, the postanhepatic phase begins, often characterized by marked changes in the patient's status. The most dramatic changes in hemodynamic parameters usually occur upon reperfusion, with hypotension and the potential for serious arrhythmia. Severe coagulopathy may also develop because of the release of natural anticoagulants from the ischemic liver or active fibrinolysis. Both epsilon aminocaproic acid and aprotinin have been used prophylactically to prevent fibrinolysis and decrease transfusion requirements [27]. Electrolyte abnormalities, most commonly hyperkalemia and hypercalcemia, are often seen after reperfusion; they are usually transient and respond well to treatment with calcium chloride and sodium bicarbonate. After reperfusion of the liver, the final anastomosis is performed, establishing biliary drainage. The recipient's remaining common

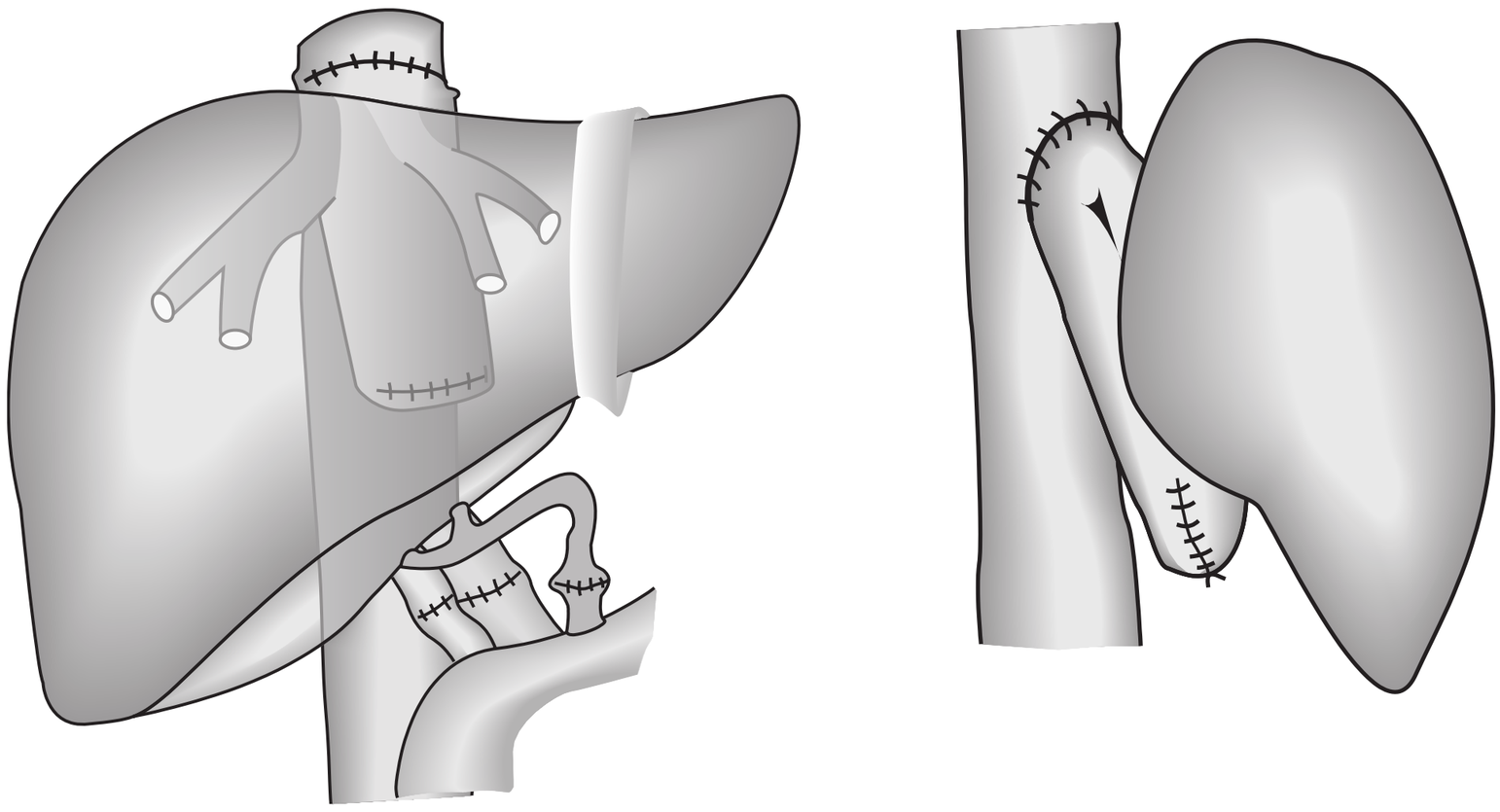

FIGURE 187.2. Illustration of "piggyback" liver transplant procedure with preservation of the recipient's inferior vena cava.

bile duct (choledochoduodenostomy) or a loop of bowel (choledochojejunostomy) may be used.

Several variations of the standard operation have been described, including the "piggyback technique." Here the recipient's inferior vena cava is preserved, the infrahepatic donor cava is oversewn, and the suprahepatic cava is anastomosed to the confluence of the recipient hepatic veins (Fig. 187.2). With this technique, the recipient's cava does not have to be completely crossclamped during anastomosis—thus allowing blood from the lower body to return to the heart uninterrupted, without the need for VVB. In spite of the potential advantages of the "piggyback technique," this procedure is precluded, for obvious reasons, in patients with tumors involving retrohepatic vena cava or main hepatic veins.

The surgical procedure for children does not differ significantly from that for adults. However, the size of the recipient is a significantly more important variable and has an impact on both the donor and the recipient operations.

For pediatric patients (especially infants and small children), the chance of finding a size-matched cadaver graft may be very small: the vast majority of cadaver donors are adults. Accordingly, pretransplant mortality used to be very high in pediatric patients. As a result, three procedures evolved from the principle that a liver is made up of several self-contained segments, each with its own vascular inflow, vascular outflow, and biliary drainage. As a result of these three procedures (namely, reduced-size liver transplants, living related liver transplants, and split-liver transplants), pediatric waiting list mortality rate is now very low.

Reduced-Size Liver Transplants

The earliest efforts involved tailoring a whole-cadaver graft on the back table to fit the recipient. A portion of the liver, such as the right lobe or extended right lobe, was resected and discarded. The remaining left lateral segment was then used for transplant. Reduced-size liver transplant (RSLT) significantly reduced waiting times for children, but negatively affected the adult recipient pool.

Living Donor Liver Transplant

Living donor liver transplant (LDLT) is a natural extension of RSLT. Usually, the left lateral segment from an adult is used (Fig. 187.2), providing sufficient liver tissue for children up to 25 kg. Advantages include the ability to perform the transplant before the recipient deteriorates clinically and the ability to select an ideal donor. The main disadvantage, obviously, is the risk to the donor.

Split-Liver Transplants

With this technique, an adult cadaver liver is divided into two functional grafts: the left lateral segment (which can be transplanted into a child) and the remaining right trisegment (which can be transplanted into an adult). Most split-liver transplants (SLTs) are now performed in vivo: the liver is divided in the cadaver, in a similar fashion to the LDLT procedure. SLT overcomes the disadvantages of both LDLT and RSLT while increasing the donor pool.

Because the severe shortage of organs, partial transplants, either a living donor transplant or a deceased donor split-liver transplant, are being increasingly used for adult recipients also. Usually, in LDLTs for pediatric recipients, the left lateral segment is used; for adult recipients, however, this would be inadequate liver mass and so usually the right lobe is used. Split-liver transplants from deceased donors involve dividing the donor liver into two segments, each of which is subsequently transplanted.

The greatest advantage of a LDLT is that it avoids the waiting time seen with deceased donor organs. In the United States, over 16,500 people are now waiting for liver transplants, but only 6,000 transplants are performed every year (UNOS/OPTN, www.optn.transplant.hrsa.gov/, accessed August, 2009) [6]. Approximately, 15% to 25% of the candidates will die of their liver disease before having the chance to undergo a transplant. For those who do end up receiving a transplant from a deceased donor, the waiting time can be significant, resulting in severe debilitation. With a LDLT, this waiting time can be bypassed, allowing the transplant to be performed before the recipient's health deteriorates further. In 2007, 266 LDLTs were performed in the United States, accounting for 4% of the total liver transplants performed that year.

A partial hepatectomy in an otherwise healthy donor is a significant undertaking, so all potential donors must be very carefully evaluated. Detailed medical screening must ensure that the donor is medically healthy; radiologic evaluation must ensure that the anatomy of the donor's liver is suitable; and a psychosocial evaluation must be done to ensure that the donor is mentally fit and not being coerced. The decision to donate should be made entirely by the potential donor after careful consideration of the risks and of the potential complications, with no coercion from anyone.

The overall incidence of donor complications after living donor liver donation ranges from 5% to 10%. There is also a small risk (<0.5%) of death [28,29]. Of note, mortality is higher for adult-to-adult donation (0.24% to 0.4%) compared with adult-to-child donation (0.09% to 0.2%). This is explained by the fact that adult-to-child donation usually removal of a smaller portion of the liver. Bile duct problems are the most worrisome complication after donor surgery. Bile may leak from the cut surface of the liver or from the site where the bile duct is divided. That site may later become strictured. Generally, bile leaks resolve spontaneously with simple drainage. Strictures and sometimes bile leaks may require an ERCP and stenting. If the above measures fail, a reoperation may be required. Intra-abdominal infections developing in donors are usually related to a biliary problem. Other complications after donor surgery may include incisional problems such as infections and hernias. The risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) is the same as for other major abdominal procedures.

The recipient operation with LDLTs is not greatly different from whole-organ deceased donor liver transplants. The hepatectomy is performed in a similar fashion—the cava should be preserved in all such cases, because the graft will generally only have a single hepatic vein for outflow. This is then anastomosed directly to the recipient's preserved vena cava. Outflow problems tend to be more common with partial versus whole transplants, especially with right lobe transplants (which, again, are usually used for adult recipients). Various methods have been described to improve the outflow of the graft, such as including the middle hepatic vein with the graft, reimplanting accessory hepatic veins, and reimplanting large tributaries that drain the right lobe into the middle hepatic vein [30–32]. Inflow to the graft can be reestablished by anastomosing the donor's hepatic artery and portal vein branch to the corresponding structures in the recipient.

Another method to increase the number of liver transplants is to split the liver from a deceased donor into two grafts, which are then transplanted into two recipients [33]. Thus, a whole adult liver from such a donor can be divided into two functioning grafts. The vast majority of split-liver transplants have been between one adult donor and two pediatric recipients. Splitting one adult liver for two pediatric recipients has no negative impact on the adult donor pool, but it does not increase it either. Adults now account for the majority of patients awaiting a transplant—and the majority of patients dying on the waiting list. Therefore, if split-liver transplants are to have a significant impact on waiting list time and mortality, they must be performed so that the resulting two grafts can also be used in two adult recipients [34]. The worry is that the smaller of the two pieces would not be sufficient to sustain life in a normal-sized adult. However, with appropriate donor and recipient selection criteria, a small percentage of livers from deceased donors could be split and transplanted into two adult recipients.

Recently, the use of organs from donors after cardiac death (also referred as non-heart–beating donors) has emerged as an important source of organs in response to the significant growth of the waiting list. DCD involves those donors who present a severe neurological injury and/or irreversible brain damage but still have minimal brain function. Therefore, DCD offers the patient and the family the opportunity to donate when criteria for brain death will not have been met [7–9]. Two different types of DCD are described. Controlled DCD involves planned withdrawal of ventilatory and organ-perfusion support, most often in the operating room with a surgical team readily available (Maastricht III). In contrast, uncontrolled DCD sustains an unexpected cardiopulmonary arrest and either fails to respond to resuscitation or is declared dead on arrival to the hospital (Maastricht I, II, and IV). The number of DCD liver allografts has gradually increased, and now represents approximately 5% of all liver transplants performed in the United States. In 2000, only 11 centers used DCD livers, increasing to 62 centers in 2007 [8].

Because of the constant imbalance between the number of available organs and the number of candidates for liver transplant, organs that were previously thought to be associated with an unacceptably high risk of initial poor function have been used to increase the donor pool. These organs obtained from the so-called expanded criteria donors have been used with an increase rate of primary nonfunction (PNF).

In 2006, a retrospective study using characteristics of more than 20,000 donors identified several factors that were associated with an increase risk of graft loss. These factors were used to generate a "donor risk index," which is directly related to a predicted rate of graft survival. Six donor/graft characteristics are as follows: (1) donor age over 40 (particularly over 60), (2) donation after cardiac death, (3) African American race, (4) shorter in height, (5) cerebrovascular accident as cause of death and (6) use of partial grafts, were significantly associated with graft failure. In parallel to the recipient risk score (i.e. MELD score) the donor risk index may help to optimize the donor/recipient matching. However, the potential benefit of utilization of this score in organ allocation remains to be determined [35].

Postoperative Care

The postoperative course can range from smooth to extremely complicated, depending mainly on the patient's preoperative status and the development of any complications. The care of all such patients involves (1) stabilization and recovery of the major organ systems (e.g., cardiovascular, pulmonary, renal); (2) evaluation of graft function and achievement of adequate immunosuppression; and (3) monitoring and treatment of complications directly and indirectly related to the transplant.

Initial Stabilization

The initial care immediately posttransplant should be performed in an intensive care unit (ICU) setting. Recipients generally require mechanical ventilatory support for the first 24 to 48 hours. The goal is to maintain adequate oxygen saturation, acid base equilibrium, and stable hemodynamics. Guidelines for extubation are no different from the standard postoperative patient: a level of consciousness sufficient to protect the airway and the ability to maintain adequate oxygenation and ventilation. As well, there should be some indication of function of the new graft prior to attempting extubation. After extubation, it is crucial to continue with aggressive physiotherapy, deep breathing exercises, and ambulation to reduce the typically high incidence of respiratory complications.

Continuous hemodynamic monitoring should be maintained via an arterial line and pulmonary artery catheter. Information obtained should be used to ensure adequate perfusion of the graft and vital organs. The preoperative hyperdynamic circulatory state will often persist into the postoperative period. Later, as hepatic function improves, the cardiac index progressively declines and the SVR increases toward normal values. However, the myocardial dysfunction that is often seen early in the reperfusion phase may persist, with decreased compliance and contractility of the ventricles. The cause of this myocardial depression is unclear, but may be related to the release of vasoactive substances after reperfusion of the ischemic liver and decompression of the portal circulation. The usual treatment is to optimize preload and afterload, and inotropic agents such as dopamine or dobutamine.

To assess for possible bleeding, serial hematocrits should be measured initially every 4 to 6 hours. Coagulation parameters

(prothrombin time, partial thromboplastin time, thrombin time) need to be carefully monitored because of frequent coagulopathy, most likely related to intraoperative blood loss and temporary ischemic damage in the revascularized new liver. Other laboratory values to monitor include serum transaminases and serum bilirubin. Normalization of these values, along with improvement in mental status and renal function, are valuable indicators of good graft function.

Fluid management, electrolyte status, and renal function require frequent evaluation after surgery. Most liver recipients have an increased extravascular volume but a reduced intravascular volume. Attention should be given to the potassium, calcium, magnesium, phosphate, and glucose levels. Potassium may be elevated because of poor renal function, residual reperfusion effect, or immunosuppression medications. Diuretics may be required to remove excess fluid acquired intraoperatively, but may result in hypokalemia. Magnesium levels should be kept more than 2 mg per dL to prevent seizures and phosphate levels between 2 and 5 mg per dL for proper support of the respiratory and alimentary tracts. Marked hyperglycemia may be seen secondary to steroids, and should be treated with insulin. Hypoglycemia is often an indication of poor hepatic function.

Nasogastric suction is initially required until normal bowel function resumes (usually 48 hours); patients with a choledochojejunostomy may need more time. Some form of prophylaxis for GI bleeding should be maintained as the physiologic stress after a liver transplant may lead to gastric erosions and ulcerations. The GI tract can be used for nutrition by postoperative day 3 to 5. However, for patients with prolonged ileus or significant intestinal edema—especially if they were malnourished preoperatively—total parenteral nutrition (TPN) should be instituted early.

As soon as the patient enters the ICU, prevention, prophylaxis, and close monitoring of possible infections should begin. Given the magnitude of the operation, the often poor pretransplant medical status, and the need for immunosuppression, it is not surprising that more than 50% of liver recipients develop some infection. Close attention must be given to all invasive monitoring lines, which should be changed every 5 to 7 days. Aggressive pulmonary toilet is needed: the lung is a common source of infection. Perioperative antibiotics with activity against biliary tract pathogens should be employed. All recipients should also receive trimethoprim–sulfamethoxazole to reduce the likelihood of infections secondary to *Pneumocystis* or *Nocardia*. Prophylaxis is also indicated against fungal infections (most commonly *Candida* and *Aspergillus*) and viral infections (most commonly CMV [cytomegalovirus] and herpes virus).

Graft Function and Immunosuppression

A crucial aspect of postoperative care is the repeated evaluation of graft function, which in fact begins intraoperatively, soon after the liver is reperfused. Signs of hepatic function include good texture and color of the graft, evidence of bile production, and restoration of hemodynamic stability. Once the patient arrives in the ICU, evaluation of hepatic function is continued based on clinical signs and laboratory values. The patient who rapidly awakens from anesthesia and whose mental status progressively improves likely has a well-functioning graft. Laboratory values that corroborate good function include normalization of the coagulation profile, resolution of hypoglycemia and hyperbilirubinemia, and clearance of serum lactate. Adequate urine production and good output of bile through the biliary tube (if present) are also indicators of good graft function. Serum transaminase levels will usually rise during the first 48 to 72 hours secondary to preservation injury, and then should fall rapidly over the next 24 to 48 hours.

Induction immunosuppression posttransplant varies from center to center. Many use a triple immunosuppressive regimen based on cyclosporine or tacrolimus, prednisone, and azathioprine or mycophenolate mofetil. Some centers also use antilymphocyte antibody for induction therapy, either for all recipients or only for those with renal dysfunction. The newer humanized monoclonal antibodies (basiliximab or daclizumab) are also being used, usually as part of regimens that involve the withholding of calcineurin inhibitors or steroids [36].

Posttransplant Surgical Complications

Given the magnitude of the operation, surgical complications posttransplant are not uncommon. One important aspect, then, of postoperative care is to be aware of any complications so that they may be quickly recognized and treated. Surgical complications related directly to the operation include postoperative hemorrhage and problems with any of the five anastomoses (five vascular and one biliary).

Postoperative Hemorrhage. Bleeding is common in the postoperative period, and is usually multifactorial. Previously, it has been reported that 15% of patients required a reoperation for bleeding control after transplant. Currently, with the improvement of postoperative treatment of coagulopathy in the ICU, the incidence of reoperation has dropped to 5%. A large raw surface is created during the recipient hepatectomy, often in a patient with significant vascular collaterals secondary to portal hypertension. A number of small persistent bleeding sites may often result. This may be compounded by an underlying coagulopathy resulting from deficits in one or more of the main systems of hemostasis: coagulation, fibrinolysis, and platelet function.

Large volume intraoperative blood transfusions and poor postoperative liver function secondary to ischemic damage of the liver can lead to severe coagulation defects. As liver function improves, coagulation parameters normalize. Fresh frozen plasma (FFP) and cryoprecipitate are used, as needed, until graft function is adequate. Thrombocytopenia is seen in virtually all recipients posttransplant, with lowest levels on postoperative day 3 and 4, then returning to normal by day 7. Platelets are transfused, as needed, for platelet counts less than 50×10^9 per L (depending on the degree of ongoing bleeding), but counts may not increase, because of ongoing deposition of platelets in the spleen. Hyperfibrinolysis, often a problem intraoperatively during the reperfusion phase, may persist into the early postoperative period. Aprotinin, a serine protease inhibitor, may be administered intraoperatively; it decreases hyperfibrinolysis-triggered bleeding in some recipients.

Blood loss should be monitored through the abdominal drains and with serial measurements of hemoglobin and central venous pressures. If bleeding persists despite correction of coagulation deficiencies, an exploratory laparotomy should be performed. Reexploration is especially important if increasing abdominal pressure is evident which may compromise respiratory or renal function. Bleeding complications are generally higher in recipients of reduced-size, split-liver, or living related grafts, because the cut surface of the liver is an additional source of potential blood loss.

Vascular Complications. The incidence of vascular complications after liver transplant is 5% to 10%. Thrombosis is the most common early event; stenosis, dissection, and pseudoaneurysm formation are less common. Any of the four vascular anastomoses may be involved, but the hepatic artery is most common [37].

Hepatic artery thrombosis (HAT) has a reported incidence of 3% to 5% in adults and about 5% to 8% in children. Several risk factors have been reported for early HAT CMV mismatch

(seropositive donor liver in seronegative recipient), retransplantation, use of arterial conduits, prolonged operation and cold ischemic times, low recipient weight, severe rejection, variant arterial anatomy, and low-volume transplantation centers. Technical factors that disturb laminar flow of the blood in the arteries (such as intimal dissection, tension on the anastomosis, and kinking of the artery) are also implicated in the development of HAT. Thrombosis rates are higher after split-liver and living related transplants, because of the smaller caliber of vessels and the sometimes complex arterial reconstruction required [38,39].

After HAT, liver recipients may be asymptomatic or they may have severe liver failure secondary to extensive necrosis. Those with thrombosis early postoperatively, especially adults, have the most dramatic signs and symptoms: marked elevation of serum transaminase levels, septic shock, HE, and overall rapid deterioration. Ultrasound with Doppler evaluation is the initial investigation of choice, with more than 90% sensitivity and specificity. Prompt reexploration with thrombectomy and revision of the anastomoses is indicated if the diagnosis is made early. If hepatic necrosis is extensive, a retransplant is indicated. CT or MRI scans may be helpful in determining the extent of necrosis. Some centers have used implantable Doppler probes performing continuous flow monitoring in patients with high risk for development of HAT.

HAT may also present in a less dramatic fashion. The donor bile duct receives its blood supply from the hepatic artery. Thrombosis may therefore render the common bile duct ischemic, resulting in a localized or diffuse bile leak from the anastomosis, or more chronically a diffuse biliary stricture. Late thrombosis may be asymptomatic, especially in children, because of the presence of collaterals (which provide sufficient arterial inflow) along the biliary anastomosis.

Thrombosis of the portal vein is far less frequent (compared with the hepatic artery), occurring in fewer than 2% of recipients. It may be related to a technical factor such as narrowing of the anastomosis or excessive length of the portal vein with kinking. Recipients who require a venous conduit secondary to underlying portal vein thrombosis are also at higher risk for portal vein thrombosis. As with HAT, clinical presentation can vary. Early postoperatively, portal vein thrombosis may result in severe liver dysfunction. Tense ascites and variceal bleeding may be seen secondary to acutely elevated portal and mesenteric venous pressures. If these symptoms develop postoperatively, urgent ultrasound with Doppler evaluation is performed to assess the patency of the portal vein. If the diagnosis is made early, operative thrombectomy and revision of the anastomosis may be successful. If thrombosis occurs late, liver function is usually preserved due to the presence of collaterals. In this case, a retransplant is not necessary, and attention is diverted toward relieving the left-sided portal hypertension.

Complications of the hepatic veins (such as thrombosis and stenosis) are rare, with an incidence of less than 1%. Recurrence of Budd–Chiari syndrome and technical factors such as narrowing of the anastomosis are the most common causes. Presentation is usually with massive ascites and graft dysfunction. Again, ultrasound Doppler will usually demonstrate the problem. The risk of thrombosis is higher in recipients of a left lateral segment, either from a living donor or as part of a split-liver graft. This segment may be quite mobile, and if it is not properly aligned, it may twist on the anastomosis, obstructing flow [40].

Biliary Complications. Complications of the biliary system continue to be common after liver transplantation. The incidence is 10% to 25% with an associated mortality of less than 5% [41]. This incidence may be even higher in partial transplant recipients and recipients of DCD livers. Biliary complications manifest as either a leak or an obstruction. Timing will often determine type and clinical outcome of the complication. Bile leaks tend to occur early postoperatively and often require surgical repair, while obstruction usually occurs later and can often be managed with radiologic or endoscopic techniques.

Most bile leaks occur within the first 30 days posttransplant. Most centers have abandoned the use of external T-tube stents because a leak may occur from the T-tube site when it is removed. In whole liver transplant recipients, biliary leaks occur most commonly at the anastomotic site. The area around the anastomosis has the most tenuous blood supply: both the donor common bile duct (CBD) and the recipient portion of the CBD are supplied by end arteries. Excessive dissection or cauterization around the donor or recipient CBD can further disrupt the blood supply, leading to ischemic complications. Another important cause of biliary tract complications is hepatic artery thrombosis: the donor CBD receives its blood supply from the hepatic artery. With any biliary tract complication, the hepatic artery should be carefully assessed to document patency. Other causes of leaks include poorly placed sutures, excessive number of sutures, and tension on the anastomosis. With partial transplants, the cut surface of the liver represents the most common site for a bile leak.

Clinical symptoms of a bile leak include fever, abdominal pain, and peritoneal irritation. Bile in the abdominal drains is highly suspicious for a leak, but absence of bile in the drains does not preclude the diagnosis. Blood tests may demonstrate an elevation of the white blood cell count, bilirubin, and alkaline phosphatase; unfortunately, no laboratory test is pathognomonic. Ultrasound may demonstrate a fluid collection, but often cholangiography is required for diagnosis. This is simple to perform if an external biliary stent is in place. In the absence of an external stent, options include magnetic resonance cholangiography (MRC), endoscopic retrograde cholangiography (ERC), or percutaneous transhepatic cholangiography (PTC).

Many recommend operative treatment for all early bile leaks. The anastomosis is revised, or for small leaks, additional sutures are placed at the leak site. If there is undue tension in recipients with a CDC, the biliary anastomosis is converted to a CDJ. The increasing popularity of treating nontransplant biliary leaks with endoscopically placed stents has led to their use for transplant-related leaks.

Biliary obstruction is usually secondary to stricture and occurs later in the postoperative period. It is most common at the anastomotic site and is likely related to local ischemia. Nonanastomotic strictures usually have a worse prognosis; they are associated with hepatic artery thrombosis, prolonged cold ischemic times, and ABO-incompatible donors [42]. Patients sustaining biliary obstruction usually present with cholangitis or cholestasis, or both. Ultrasound can be misleading in making the diagnosis, since ductal dilatation may not be seen; however, it is still a crucial test in order to exclude potential hepatic arterial flow complication (which is a potential cause of bile duct stricture). Cholangiography (T-tube cholangiography, ERC, MRC, or PTC, depending on the type of BD reconstruction performed) is always necessary for diagnosis of BD stricture. The treatment is usually not an operation, but rather by percutaneous on internal balloon dilatation and stent placement across the site of stricture. If these initial options fail, surgical revision is required.

Wound Complications. Wound complications, very common in liver transplant recipients, can be a source of significant morbidity. In the general surgical population, risk factors for wound complications have been well described, including a lengthy operative procedure, bowel or biliary contamination, blood transfusions, poor nutritional status, and steroid administration. All of these risk factors are generally present in liver recipients.

The most common problems with the wound are infections and hematomas. Direct bacterial contamination of the wound may occur from bile or bowel contents if a CDJ is performed. Wound hematomas can easily result from large abdominal wall collaterals, compounded by underlying coagulopathy. Wound infections will usually present after postoperative day 5. The infection may be obvious, with fever, chills, erythema, and purulent drainage from the wound. But at times, signs and symptoms may be minimal. Treatment is the same as for nontransplant patients: opening the wound, serial dressing changes, and allowing healing by secondary intention. IV antibiotics should be used with significant cellulitis or systemic symptoms. Necrotizing fasciitis has also been reported, and requires rapid, aggressive debridement plus high-dose IV antibiotics.

Posttransplant Medical Complications

Given the underlying illness and the need for powerful immunosuppression, it is not difficult to see why a significant percentage of liver recipients develop some medical complication before discharge. Medical complications seen early posttransplant may be due to immunosuppression, to residual effects of the liver failure, or to unrelated factors. Almost any organ system may be involved.

Nontechnical Graft Dysfunction. The vascular and biliary complications described earlier can all lead to poor liver function postoperatively. Hepatic dysfunction not related to technical complications may also be seen during this time. Causes may include PNF of the graft, acute rejection, and infection.

PNF is a devastating complication, with a mortality rate of more than 80% without a retransplant. By definition, it is a syndrome that results from poor or no hepatic function from the time of the transplant procedure. Most centers now report the incidence to be less than 5%.

The cause of PNF is unknown, but several retrospective studies have attempted to identify donor risk factors that may predict development of this syndrome. Donor factors that have been associated with PNF include advanced age, increased fat content of the donor liver, longer donor hospital stay before organ procurement, prolonged cold ischemia (> 18 hours), and reduced-sized grafts [43].

Early prediction of PNF is valuable in identifying patients that will need a retransplant. It is also important to rule out conditions that may mimic PNF such as hepatic artery thrombosis, accelerated acute rejection, and severe infection. Intraoperative clues may indicate poor graft function. PNF should be considered in recipients who do not stabilize soon after reestablishment of hepatic perfusion, or who have ongoing hemodynamic instability, worsening acidosis and coagulopathy, poor bile production, or poor liver graft color. Upon arrival to the ICU, recipients who do not regain consciousness, or who have increasing renal dysfunction, continued hemodynamic instability, increasing prothrombin time, or persistent hypoglycemia may have PNF. An AST > 5,000 IU per L, Factor VIII < 60% of normal, PT > 20 seconds at 4 to 6 hours postreperfusion, in association with poor bile production, may all suggest PNF.

Unfortunately, no medical treatment is effective for PNF. IV prostaglandin E1 (PGE1) has some useful effect [44], but further evaluation is necessary. Its mechanism of action is presumably a vasodilatory effect on the splanchnic circulation, resulting in enhanced blood flow to the new liver. PGE1 is also immunomodulatory and may lessen the risk of graft rejection. Recipients with suspected PNF should probably be started on a continuous infusion and listed for an urgent retransplant. The starting dose is 0.005 µg per kg per minute, which is increased, as tolerated per blood pressure measurements, to a maximum of 0.03 µg per kg per minute. Ultimately, such recipients do better with a retransplant. However, if a retransplant is to positively influence outcome, it must be done before multiorgan failure develops. In one series of 15 liver recipients with PNF, all those who sustained organ failure in four or more systems died despite a retransplant [45].

Rejection is very common after a liver transplant; 20% to 30% of recipients will have at least one bout at some point posttransplant. Most acute rejection episodes are not seen until at least 1 week posttransplant. Rejection episodes during the first posttransplant week may be seen in recipients of ABO-incompatible grafts, or those with a very strongly positive preoperative cytotoxic cross-match. With current immunosuppressive drugs, signs and symptoms of acute rejection tend to be fairly mild. Most commonly, the serum bilirubin and/or transaminase levels are elevated, which may be completely asymptomatic or may involve mild accompanying symptoms such as fever and malaise. The differential diagnosis must include mechanical complications (such as vascular thrombosis and bile leaks), and underlying sepsis. Ultimately, a histologic assessment of the graft is required to confirm the diagnosis of acute rejection, most commonly via a percutaneous liver biopsy. Mild rejection episodes can usually be treated simply by increasing the level of maintenance immunosuppression. Episodes that are judged to be moderate or severe by histology are usually treated with high-dose IV corticosteroids.

Neurologic Complications. Neurologic complications posttransplant are common, affecting more than 20% of liver recipients. Complications generally manifest as decreased level of consciousness, seizures, or focal neurologic deficits.

Decreased level of consciousness is usually due to oversedation from drugs that have accumulated over days because of impaired hepatic or renal clearance. Benzodiazepines and narcotics are common culprits, but unresponsiveness may also be secondary to calcineurin neurotoxicity. This tends to be more common in patients with previous hepatic encephalopathy.

Multiple metabolic abnormalities are frequent posttransplant, and may diminish alertness. A poorly functioning or nonfunctioning graft with resulting liver failure can lead to hepatic encephalopathy. Other evidence of liver failure is also frequent, such as a marked elevation of liver enzymes, prothrombin time, and ammonia levels. Flumazenil, a benzodiazepine receptor antagonist, improves HE for a short time [46]. It may thus be a useful diagnostic tool when HE is suspected, postoperatively. Renal failure and sepsis may also contribute to a metabolic encephalopathy. After significant periods of perioperative hypotension, a decreased GCS may indicate hypoxic-ischemic encephalopathy. This may be a difficult diagnosis to make, since imaging studies are often normal. Nonspecific abnormalities may be seen on EEG. The clinical scenario is characterized by an initial insult, then a prolonged recovery period, often characterized by decreased alertness.

Central pontine myelinolysis (CPM) is an uncommon cause for failure to awaken posttransplant [47]. Typically, it is seen with marked fluctuations in serum sodium levels and osmolality, or in recovered alcoholics. CT is often normal, but MRI may demonstrate characteristic abnormalities in the pons. Careful attention to shifts in the serum sodium and osmolality may decrease the risk of CPM.

FHF patients, especially those with severe HE and evidence of cerebral edema preoperatively, invariably have a period of diminished level of consciousness posttransplant. Intraoperatively, during the reperfusion phase, their intracranial pressure (ICP) often increases. If untreated and severe, this increase may lead to neurologic death, which is often not diagnosed until in the ICU. Usually, however, the effects of cerebral edema linger over a period of 7 to 10 days postoperatively, with eventual recovery. ICP monitoring pre- and intraoperatively may be of value in detecting cerebral edema and marked elevations of pressure.

Liver recipients, who have an initially normal neurologic course postoperatively, followed by sudden clinical deterioration, should be evaluated for an intracranial hematoma. Predisposing factors include underlying coagulopathy and systolic hypertension.

Postoperative seizures usually occur de novo, tend to be of the generalized tonic clonic variety, and are most common during the first 2 weeks posttransplant. Causes are numerous. Electrolyte abnormalities (such as hyponatremia, hypocalcemia, and hypomagnesemia) and medications, are the most common causes. Structural abnormalities such as intracranial hemorrhage and cerebral infarction may be responsible. Infectious processes (such as meningitis, encephalitis, and a brain abscess) should also be considered.

Immunosuppression medications may sometimes cause significant neurologic changes after transplantation. Several neurotoxic effects have been associated with use of cyclosporine, including tremors, headache, mental status changes, seizures, focal neurological deficits, and/or visual disturbances. Tacrolimus produces neurologic disorders similar to those seen in patients using cyclosporine, but more frequently. Posterior reversible encephalopathy syndrome (PRES) is a rare but serious complication of immunosuppressive therapy after solid organ transplantation (0.5%). In addition to the neurologic symptoms, which range from headaches to mental status changes, this syndrome is associated with a characteristic imaging feature of subcortical white matter lesions on magnetic resonance imaging. The changes in the subcortical white matter are secondary to potentially reversible vasogenic edema. These imaging findings predominate in the territory of the posterior cerebral artery. PRES typically develops in the first 2 months after liver transplantation (90%). A prompt diagnosis of this rare entity with a temporary discontinuation of the calcineurin inhibitor offers the best chance of avoiding long-term sequelae [48].

Cardiovascular Complications. A number of cardiovascular complications (including arrhythmia, ischemia, changes in blood pressure and cardiac arrest) can be seen intra- and postoperatively. They may occur in liver recipients with previously normal cardiac status or in those with underlying comorbid cardiac conditions. The latter group is becoming more important as the increased success of liver transplantation has led to expanded indications and older recipients.

Most intraoperative cardiovascular complications are seen immediately after reperfusion of the liver. About 30% of recipients experience a transient decrease in blood pressure during this phase, which has been termed the postreperfusion syndrome (PRS). This syndrome is defined by a decrease in the mean arterial pressure of at least 30% for 1 minute within the first 5 minutes after reperfusion, accompanied by a decrease in the heart rate and SVR and an increase in the CVP and PCWP. The exact cause of the myocardial depression and decreased contractility seen with PRS is unclear, but is likely multifactorial. Hyperkalemic, cold, acidotic fluid washed out from the graft, combined with existing abnormalities such as hypocalcemia and acidosis, may be the main culprits. Myocardial depressant factors may also be released from the ischemic graft on reperfusion. The effect is generally short-lived; left ventricular function is usually normal within 5 minutes. Some recipients, however, experience extreme bradycardia and hypotension, leading to cardiac arrest; this is rare and small doses of inotropic agents are usually effective. Arrhythmias, such as ventricular tachycardia and ventricular fibrillation, have also been described in the early reperfusion phase.

The incidence of postoperative myocardial ischemia is 5% to 13%. As the age of transplant candidates has increased, so has the likelihood of silent coronary artery disease, leading to perioperative ischemia. Candidates with risk factors and a high probability of coronary artery disease should undergo a pretransplant coronary assessment. Poor exercise tolerance often precludes a formal stress test. Pharmacological stress testing with either dipyridamole thallium imaging or dobutamine echocardiography, may be better. Candidates with positive tests should undergo coronary angiography, with a view toward revascularization procedures (PTCA, CABG) as indicated.

A rare postoperative complication is acute right ventricular failure secondary to severe pulmonary hypertension, but deaths have been reported [49]. The pulmonary hypertension in these recipients was likely present pretransplant. It is an uncommon complication of portal hypertension, affecting less than 1% of patients. The exact cause is unclear, though portal hypertension is the strongest predisposing factor. Histologically, the predominant lesion is a nonspecific plexiform arteriopathy. Pretransplant right heart catheterization may be necessary to establish the diagnosis; severe pulmonary hypertension may contraindicate transplantation.

Pulmonary Complications. The pulmonary system is one of the most common sites of complications posttransplant; infectious and noninfectious pulmonary complications may be seen. Infectious complications predominate after the first posttransplant week, but noninfectious complications (such as pulmonary edema, pleural effusions, atelectasis, and ARDS) predominate prior to that.

Mechanical ventilation, generally short-lived, is required immediately posttransplant in almost all liver recipients. Most patients can be extubated within the first 48 hours. Those with significant preoperative lung disease, malnutrition, or early postoperative pulmonary and hepatic complications tend to require prolonged intubation.

Atelectasis is very common posttransplant, as it is after other major abdominal operations. Significant preoperative ascites and pleural effusions are predisposing factors. Poor nutrition, decreased level of consciousness, and poor lung compliance are other contributing factors. Treatment is generally successful with chest physiotherapy and PEEP, with therapeutic bronchoscopy reserved for recipients with large areas of collapse or persistent atelectasis. Diaphragmatic dysfunction may also be seen posttransplant, with resultant right-sided atelectasis and decreased vital capacity, which may prolong the need for ventilatory support. The cause of this dysfunction is probably a crush injury of the right phrenic nerve, which can occur during surgery when the suprahepatic caval clamp is applied [50]. Usually, the nerve and diaphragmatic function completely recover, but it may take up to 9 months posttransplant.

Pleural effusions are noted in a large number of recipients. The right side is more commonly involved. Usually transudative in origin, pleural effusions may be related to sympathetic fluid accumulation from the operative diaphragmatic dissection or preoperative ascites. Typically, these effusions resolve spontaneously within 1 to 2 weeks. Thoracentesis may be needed to rule out an empyema or hemothorax. If the effusion is large enough to compromise respiratory status, therapeutic thoracentesis or insertion of a small pigtail catheter for drainage should be performed.

All of the above conditions may manifest with arterial hypoxemia postoperatively. A less common cause of hypoxemia is the presence of intrapulmonary vascular dilatations (IPVD). These vascular abnormalities are sometimes seen in patients with chronic liver disease, associated with portal hypertension and spider angiomas of the skin. Common clinical findings are dyspnea, cyanosis, clubbing, exercise desaturation, and orthodeoxia. Two techniques are generally used to confirm intrapulmonary vascular dilatation: transthoracic contrast-enhanced echocardiography, and perfusion body scan with

99mTechnetium-labeled macroaggregated albumin (99mTc-MAA). During transthoracic contrast-enhanced echocardiography, IV injections of microbubbles (diameter < 90 μm) are used to visualize intrapulmonary shunts. The timing of the appearance of the microbubbles in the left side of the heart makes the distinction between intracardiac and intrapulmonary shunts. Whole-body scan with 99mTechnetium-labeled macroaggregated albumin allows not only the detection of IPVD, but also its quantification. In normal individuals the macroaggregates (> 20 μm in diameter), are normally trapped in the pulmonary circulation. In the presence of cardiac right-to-left shunts or intrapulmonary vascular dilatation, the uptake of 99mTc-MAA in other organs, such as the brain, kidneys, spleen, and liver, can be visualized. The major disadvantage of this technique is the inability to differentiate between intracardiac shunts and IPVD [51,52].

The combination of chronic liver disease, IPVDs, and severe hypoxemia or a markedly increased alveolar arterial oxygen gradient has been termed the hepatopulmonary syndrome (HPS). HPS is reversed in 60% to 90% cases after liver transplantation, and can be documented by a perfusion lung scan [52]. Hypoxemia, requiring supplemental oxygen, can be corrected as early as 6 to 12 months after surgery; however, an increased recovery time is shown in older patients, patients with a preoperative $PaO_2 \leq 52$ mm Hg and/or $AaPO_2 \geq 66$ mm Hg, or if the liver disease is a result of alcohol abuse [51,52].

Patients with significant hypoxemia pretransplant should be investigated for IPVDs. For those with a good response to 100% O_2, the transplant may proceed: the recipient has a good chance for improvement postoperatively. But for those with a poor response, pretransplant pulmonary angiography and embolization might be beneficial. Recipients with documented IPVDs and severe hypoxemia postoperatively may also benefit from embolization, especially if they have large discrete IPVDs.

Renal Complications. Some degree of renal dysfunction is very common after transplant, affecting almost all liver recipients. About 10% have renal failure severe enough to require dialysis. Impairment may already have been present pretransplant, or may develop early or late in the posttransplant period. Early diagnosis, identification of the cause, and appropriate interventions are necessary. Renal failure, whether pre- or posttransplant, increases the mortality rate associated with the procedure.

Postoperative renal problems that may have been present pretransplant are most commonly due to hepatorenal syndrome (HRS) or acute tubular necrosis (ATN). Usually, such problems will improve posttransplant, but recipients with severe pretransplant renal dysfunction are at greater risk for persistent renal impairment posttransplant. Those with prolonged renal impairment pretransplant, or those who are dialysis-dependent and not likely to regain kidney function after a liver transplant, should be considered for a simultaneous liver–kidney transplant. Obtaining a kidney biopsy pretransplant may help determine the reversibility of the underlying renal disease and hence the need for a combined transplant.

Intraoperatively, periods of hypovolemia and hemodynamic instability may contribute to postoperative renal dysfunction secondary to ATN. Such periods can be minimized by invasive cardiac monitoring to maintain adequate blood volumes and cardiac output. A rapid infusion technique is crucial, at times, to allow the anesthesiologist to keep pace with ongoing volume losses. Some surgeons argue that venovenous bypass (VVB) reduces renal vein pressures during the anhepatic phase when the cava is clamped, thus reducing the risk of postoperative renal dysfunction. Several centers routinely use VVB though there is no significant evidence to show a decreased incidence of postoperative renal failure. Several centers have adopted a selective policy, reserving VVB for liver recipients who meet certain criteria, such as hemodynamic instability with caval clamping or preexisting renal dysfunction. Intraoperative administration of verapamil or furosemide has been tried, but there is no good evidence of any significant renal benefit.

Postoperative renal dysfunction is often multifactorial. The cause may be prerenal, renal, or postrenal. Postrenal causes are rare and are usually easy to rule out. Prerenal and renal causes account for the vast majority of dysfunction [53].

Hypoperfusion of the kidneys will lead to a prerenal picture characterized by a low urine output, decreased sodium in the urine (< 10 mEq per L), and a fractional excretion of sodium of less than 1%. Hypoperfusion is most common with systemic hypovolemia, often due to ongoing blood loss within the abdomen. Third-space fluid losses into the area of dissection or from bowel wall edema (related to the portal vein clamping) may also lead to intravascular volume depletion and prerenal azotemia. Renal hypoperfusion may also be due to significantly raised intra-abdominal pressure, as with tense ascites or a large volume of intraperitoneal blood and clots.

True HRS will give a picture similar to other prerenal causes, as it is believed to result from renal arterial vasoconstriction. Low sodium and a low fractional excretion of sodium again characterize urinary electrolytes. Generally, HRS is present pretransplant, especially in patients with fulminant hepatic failure or acute deterioration of chronic liver failure. Classically, HRS is considered to be functional, so kidney function should fully recover posttransplant. HRS can be divided into two types (1 and 2) based on prognosis and clinical characteristics. In HRS-1, an abrupt deterioration in the renal function occurs and often develops after a precipitating event (particularly spontaneous bacterial peritonitis). HRS-2 is characterized by a steady or slowly progressive course that occurs mostly in an outpatient setting in patients with refractory ascites. Survival of patients with HRS-1 is shorter than that of patients with HRS-2. The full recovery of kidney function is usually achieved after transplant; however, renal recovery may be delayed, especially in patients with HRS-2 and if some degree of ATN was superimposed. New onset of HRS posttransplant occurs with PNF or severe graft dysfunction, and may indicate the need for an urgent retransplant [54].

Renal causes are most commonly secondary to ischemic ATN, drug nephrotoxicity, or preexisting renal disease. Urinary electrolytes generally reveal a salt-wasting picture, with a high urinary sodium level (> 30 mEq per L) and a fractional excretion of sodium > 1%. On microscopic urinalysis, granular casts may be identified in the presence of ATN. The cause of ATN in liver recipients is usually ischemia and sustained hypoperfusion of the kidneys. ATN may start preoperatively, especially in acutely ill patients, or may develop secondary to hemodynamic instability intraoperatively. In one study, the predictors of acute renal failure in the immediate postoperative period were poor preoperative clinical conditions (worse Child score), elevated basal creatinine value pretransplant, transfusion of a large volume of blood products, and intraoperative hypotension [53,54]. ATN may also be seen with sepsis and multiple organ dysfunction.

Nephrotoxicity secondary to drugs is also very common. Most liver recipients have some drop in the creatinine clearance posttransplant secondary to cyclosporine or tacrolimus, both of which have significant nephrotoxic properties. Acute renal failure may be more common with high drug levels and with intravenous formulations. These immunosuppressive agents may also worsen existing renal dysfunction. Nephrotoxicity may also be secondary to other drugs, most commonly the aminoglycosides and amphotericin B.

Once renal dysfunction is adequately diagnosed, therapy can be guided appropriately. Invasive monitoring with an arterial line and a pulmonary artery catheter is helpful to optimize hemodynamic parameters and renal perfusion. Hypovolemia

should be treated with volume replacement and blood products as necessary. Blood pressure should be kept in the normal range, as determined from preoperative values. For decreased cardiac output secondary to myocardial depression, inotropic agents such as dopamine or dobutamine are indicated. If increased SVR is the main problem, a peripheral vasodilator may be of benefit. Other interventions would depend on the cause of renal dysfunction. Tense ascites can be relieved with paracentesis, while nephrotoxic drugs should be discontinued or their dosage lowered.

Once cardiovascular parameters have been optimized and compounding factors dealt with, efforts should be made to establish diuresis. Prognosis is generally better in recipients with nonoliguric (as opposed to oliguric or anuric) renal failure. The role of diuretic therapy is unclear. Recipients who were on chronic diuretic therapy pretransplant may have "diuretic dependence," and require its continued use posttransplant to maintain urine output. They should be adequately volume-loaded before diuretics are initiated, otherwise renal failure may be exacerbated. A loop diuretic such as furosemide is often the first-line agent. Its delivery to the afferent artery of the kidney depends, in part, on its binding to albumin. Therefore, in recipients with significant hypoalbuminemia, infusion of albumin may be necessary to maximize the effect of the diuretic.

If renal function does not improve, artificial renal support may become necessary. Options include regular hemodialysis or continuous venovenous hemofiltration (CVVH). Intermittent hemodialysis may not be feasible for acutely ill postoperative patients because of the hemodynamic instability it often causes. CVVH imposes a less significant stress on the hemodynamic system. Indications for CVVH or hemodialysis include (1) significant volume overload with evidence of pulmonary edema, (2) persistent or worsening hyperkalemia, and (3) persistent or worsening metabolic acidosis.

In patients with chronic hepatitis C virus (HCV) infection who have undergone a liver transplant, kidney dysfunction can be also associated with type II mixed cryoglobulinemia. Mixed cryoglobulinemia is a systemic vasculitis secondary to circulating immune complex deposition in the small vessels, and is usually triggered by the hepatitis C virus infection. The principal clinical manifestations of glomerular disease (usually membranoproliferative glomerulonephritis, MPGN) are the presence of proteinuria and microscopic hematuria, with impaired kidney function. The diagnosis of HCV-related MPGN is usually made by positive tests for serum HCV antibodies and HCV RNA, high concentrations of cryoglobulins, positive rheumatoid factor assays, and low levels of complement [55].

Infectious Complications. Infections are common after all organ transplants, but the incidence is highest after liver transplantation. More than two-thirds of recipients will experience at least one infective episode. Several factors account for this very high incidence: (1) the length and magnitude of the operation, (2) the high potential for biliary and enteric contamination, and (3) the poor overall medical condition of many recipients.

The incidence of infections has not changed significantly since the early days of liver transplantation. What has changed is the mortality rate. Early series reported mortality rates of 25% to 50% associated with infections. More recent studies, however, suggest that infection-related deaths in most centers are now less than 10%. A better understanding of the immunosuppressed state, identification of risk factors, and more effective means of treatment and prophylaxis have all contributed to an improved prognosis. Nonetheless, infections remain the most common cause of early mortality posttransplant and a significant source of morbidity. Identification of risk factors, preventive measures and effective prophylaxis, rapid diagnosis, and prompt and appropriate treatment are all crucial.

The preoperative workup should include evaluation for any infective diseases. Serologic testing should assess the transplant candidate's CMV, HIV, and hepatitis (B and C) status. Latent infections (such as tuberculosis) that may be reactivated with immunosuppression must be ruled out. Focus should be on active infections that would require treatment pretransplant or even preclude a transplant. Candidates with chronic liver failure are prone to infections such as spontaneous bacterial peritonitis, cholangitis, pneumonia and fungal infections, all of which should be treated appropriately and documented as improved pretransplant. The urgency of the transplant will often determine the length of treatment.

Once the transplant has occurred, efforts should be instituted to prevent infections. Perioperative antibiotics effective against biliary tract pathogens are important. Other prophylactic regimens with proven benefit include trimethoprim–sulfamethoxazole for *Pneumocystis* pneumonia (other options include dapsone, atovaquone, and pentamidine), acyclovir or ganciclovir for CMV and other herpes family viruses, and nystatin or fluconazole/voriconazole for antifungal prophylaxis. Preventive measures that should be followed are no different than for similar, nontransplant patients in a critical care setting: attentive care to indwelling arterial and venous lines, change of central catheters every 7 days, and aggressive pulmonary toilet.

Any postoperative fever should prompt an urgent, thorough evaluation for infection, including culture of blood, urine, sputum, and ascitic fluid, as indicated. A CXR to rule out a pulmonary source should be performed, then bronchoscopy and lavage to evaluate any suspicious infiltrates. A thorough examination with close attention to the wound is important. A wound infection will require opening of the wound and serial dressing changes. If no obvious source of infection is found, a CT scan of the abdomen to look for fluid collections is warranted. A diagnostic aspiration can then be performed to rule out an abscess. If the recipient has a persistent high temperature or toxic appearance, antibiotics should be started, even without identification of the infective source. Generally, a wide-spectrum antibiotic with activity against biliary pathogens is the agent of first choice. Of note, an elevated temperature may also be seen with other conditions, such as acute rejection, graft-versus-host disease, and drug reactions.

Infections posttransplant are broadly categorized into those occurring early (within 1 month) and later. Regardless of the timing, bacterial, viral, or fungal pathogens may be responsible. The relative incidence of these various pathogens differs at different times posttransplant.

Bacterial and fungal organisms account for most infections during the first month. The immunosuppressed state is a risk factor, but these infections are more related to surgical complications, initial graft function, and morbid conditions that existed pretransplant. Risk factors include prolonged surgery, large-volume blood transfusions, PNF requiring a retransplant, and reoperations for bleeding or bile leaks. Common sites for these infections, in decreasing order of frequency, are the abdomen, the respiratory tract, blood, wounds, and the urinary tract.

After the first month, the immunosuppressed state becomes the main risk factor for infection. Immunosuppressive drugs depress cell-mediated immunity, leading to opportunistic infections with viral, fungal, and parasitic pathogens. The risk increases as immunosuppression increases, especially when acute rejection episodes are treated with bolus high-dose steroids or antilymphocyte agents. Bacterial infections generally decline after the first month, except in recipients who have had prolonged ICU stays because of surgical complications or respiratory failure. Other predisposing factors for late bacterial infections are a biliary stricture and hepatic arterial thrombosis.

Bacterial infections usually involve the abdominal cavity, including the wound. Bacterial pathogens often originate from either the biliary tree or from the small bowel. A choledochojejunostomy (CDJ) for biliary drainage is associated with a higher rate of infection than is a duct-to-duct biliary anastomosis. Contamination may occur either at the time of surgery, or later because of biliary complications such as a leak or stenosis. Abdominal infections usually manifest as cholangitis, abscesses (intra- or extrahepatic), peritonitis, or wound infection. Cholangitis often develops with an underlying biliary stricture and may lead to a subsequent ascending infection with development of intrahepatic abscesses. Hepatic artery thrombosis may also lead to ischemia of the allograft and development of intrahepatic abscesses secondary to necrosis of the liver. Peritonitis and an extrahepatic abscess often signal the presence of a bile leak. If an intra-abdominal infection is suspected, a CT scan should be done, with aspiration and culture of any identified fluid collections. If a biliary stent is present, it can be used to evaluate for the presence of a leak or stricture. In the absence of a stent, a nuclear medicine study or cholangiography (percutaneous or endoscopic approach) may be necessary to evaluate the biliary tree. Therapy involves drainage of the abscess, management of any identified biliary complications, and IV antibiotics directed at the most likely pathogens: aerobic Gram-negative bacilli (*E coli*, *Enterobacter, Pseudomonas*), some aerobic gram-positive cocci (group D *Streptococcus*), and anaerobes.

Fungal infections are a major cause of morbidity and death after all solid-organ transplants. Liver transplants are associated with the highest incidence of fungal infection, with some studies reporting an incidence of about 20%. The cause may be contamination from the biliary tract or small bowel during surgery. Most fungal infections are seen during the first 2 months posttransplant. Risk factors include preoperative renal dysfunction, prolonged duration of surgery, a retransplant, other reoperations, and CMV infection [56]. The vast majority of early fungal infections are secondary to *Candida* or *Aspergillus* species. Less common pathogens include *Cryptococcus* and *Trichosporon*, which are generally seen later in the transplant course because of chronic immunosuppression.

Viral infections generally are not seen until after the first posttransplant month. Common pathogens include CMV, Epstein–Barr virus (EBV), herpes simplex virus (HSV), and the hepatitis viruses (B and C). The mortality rate is generally not as high as with fungal and bacterial infections, yet viral pathogens account for significant morbidity. CMV is the most common pathogen involved. Its presentation ranges from asymptomatic infection to tissue-invasive disease. Asymptomatic infection is characterized by the shedding of virus in urine or saliva plus a change in the recipient's serostatus. CMV disease is suggested by the presence of the virus in the blood and by systemic symptoms such as fever, malaise, arthralgia, and leukopenia, with or without specific end-organ involvement (liver, lungs, bowel, eyes). Tissue-invasive CMV disease (TI-CMV) indicates organ involvement and presents as hepatitis, gastroenteritis, retinitis, or pneumonia.

The introduction and widespread use of IV ganciclovir has significantly altered the prognosis of CMV disease, which now is an uncommon cause of death posttransplant. Treatment with this drug at 10 mg per kg per day for 14 to 21 days posttransplant is effective, with minimal toxicity. Neutropenia may be seen, but usually responds to dose reduction or temporary discontinuation of the drug. If neutropenia remains a problem, then colony-stimulating factor (G-CSF) can be used. IV ganciclovir is also effective prophylaxis against CMV infections. Many different prophylaxis regimens are currently used, including high-dose oral acyclovir for 12 weeks posttransplant and, more recently, newer drugs such as oral ganciclovir, valacyclovir, and valganciclovir.

Viral hepatitis and liver transplantation are closely linked; hepatitis C is a common indication for a transplant. In the vast majority of liver recipients, however, disease eventually recurs in the new graft, representing a persistence or recurrence of preexisting infection. The risk of recurrence is now significantly lower for hepatitis B (versus C), but the former has a significantly worse prognosis. The risk of recurrence for hepatitis B depends in part on pretransplant replicative state. Recipients positive for hepatitis B viral DNA or hepatitis B e antigen have a higher risk of recurrence. Those with fulminant hepatitis B or coexisting hepatitis delta infection have lower recurrence rates. Once infection recurs, the course is characterized by rapid progression and eventual cirrhosis. A retransplant is generally not effective because of the very high recurrence rate in the second graft, especially if disease recurred in the first graft shortly posttransplant. Fortunately, recurrence rates are now very low due to the routine use of infection prophylaxis regimens which include long- and short-term administration of hepatitis B immunoglobulin with or without use of antiviral agents such as lamivudine [57].

Almost all patients transplanted for hepatitis C develop recurrent infection. The prognosis associated with recurrent hepatitis C is not as poor as with recurrent hepatitis B. Many liver recipients will show some histologic evidence of mild hepatic inflammation in the graft by 3 to 6 months posttransplant. However, only about 20% of them progress to cirrhosis requiring a retransplant. Unfortunately, prophylaxis regimens to prevent recurrent hepatitis C are not effective, and so recurrence of hepatitis C liver disease after transplant is becoming an increasingly important problem [58].

Gastrointestinal Complications. GI complications may occur as the direct result of a technical complication from the operation. Bile or enteric leaks from anastomoses can lead to generalized peritonitis or intra-abdominal abscesses. Other GI complications may result from the stress of the operation, an infection, or drug toxicity. Upper GI bleeding is usually secondary to peptic ulcer disease, persistent bleeding from esophageal varices, stress gastritis, or CMV gastroenteritis. Bleeding from gastric and esophageal varices usually settles quickly posttransplant. Persistent bleeding should trigger an assessment of the portal vein to rule out thrombosis or stenosis, which may be the underlying factor. If the recipient recently received sclerotherapy for variceal bleeding, the possibility of postsclerotherapy esophageal ulceration should be considered. Diffuse gastritis secondary to surgical stress is uncommon today, thanks to routine prophylaxis posttransplant with antacids, H2 antagonists, or proton pump inhibitors. Peptic ulcer disease remains a possible cause of upper GI bleeding. High-dose steroids seem to have some causal relationship to its development. Its incidence seems to be highest in the first month posttransplant, perhaps related to the time when steroid doses are generally highest. Ulcerations in the upper GI tract may also be due to infection. Severe esophagitis secondary to *Candida* can progress to frank ulceration with bleeding. Ulcerations may also be of viral origin, most notably CMV. Other unusual causes of GI bleeding are hemobilia after liver biopsy (incidence of 0.03%) and bleeding from the Roux-en-Y anastomosis in patients who required choledochojejunostomy.

Lower GI bleeding posttransplant is often secondary to colitis, which is of infectious origin. Usually, opportunistic pathogens such as CMV, *Clostridium difficile*, and fungi (e.g., *Candida*) are responsible. Ulcers of noninfectious origin may also cause colonic bleeding, related to the high-dose steroids used in induction therapy.

Bowel perforation is a devastating complication associated with a high mortality rate. A high index of suspicion is required. The typical signs and symptoms associated with acute peritonitis, such as a high temperature and severe pain, may be masked

or hidden by the effects of steroids. Perforation may be of the small or large bowel, with the latter associated with a higher mortality rate. Inadvertent or unrecognized injury to the bowel wall during the operation may later present as a perforation. Perforations may also be spontaneous; these are more common in children, generally occur 7 to 14 days posttransplant, and may be related to the high-dose steroids. As with perforation in nontransplant patients, early diagnosis with prompt reexploration is the best option. The leak can be repaired with irrigation of the abdominal cavity to decrease the degree of contamination.

INTESTINAL TRANSPLANTATION

Intestinal transplants have been performed in the laboratory for years. The first human intestinal transplant was performed in 1966. But it remained essentially an experimental procedure, with dismal results, well into the 1980s. Newer immunosuppressive drugs and advances in the surgical techniques have played a significant role in the successes with the procedure since the mid-1990s. Although intestinal transplants remain the least frequently performed of all transplants, graft survival rates have significantly improved and now approaching those seen with other types of extrarenal transplants. As the early problems with technical graft losses have diminished, immunologic and infectious issues have emerged as the main challenges facing the field today [59].

There are several reasons why the number of intestinal transplants has not increased as dramatically as the other transplants. As with kidney failure patients, a medical alternative exists for patients with intestinal failure, namely, long-term total parenteral nutrition (TPN). Unlike kidney failure patients, however, patients with intestinal failure have no survival advantage with a transplant (vs. medical therapy). Immunologically, the small intestine is the most difficult organ to transplant. It is populated with highly immunocompetent cells, perhaps explaining the reason for the high rejection rates and the need for higher levels of immunosuppression. Moreover, the intestinal lumen is filled with potential infective pathogens, which can gain access to the recipient's circulation if there is any breakdown of the mucosal barrier (which can occur with an acute rejection episode).

Pretransplant Evaluation

Intestinal failure is defined as the inability of the intestine to maintain nutrition or fluid and electrolyte balance without parenteral support. This most commonly results from extensive resection of the small bowel with resultant short bowel syndrome (SBS). Currently intestinal transplant is indicated for patients suffering from irreversible SBS who present with life-threatening complications secondary to the TPN or underlying disease. Traditional criteria for intestinal transplant in patients with SBS on TPN include (i) thrombosis of two major venous access sites, (ii) recurrent line infections and sepsis requiring hospitalization (more than two episodes per year), (iii) imminent liver failure related to TPN, and (iv) severe and frequent electrolyte imbalance and/or dehydration in spite of TPN [60]. At present, patients who are stable on TPN without such complications are generally not considered intestinal transplant candidates, because their estimated annual survival rate may be higher with TPN. However, as results continue to improve with transplant, this may be altered.

Other uncommon indications for intestinal transplant in patients with intestinal failure but without SBS are (i) severe myopathy or neuropathy of the GI tract (hollow visceral myopathy, total intestinal aganglionosis, pseudo-obstruction syndrome), (ii) gut malabsorption syndromes (microvillus inclusion disease, radiation enteritis, selective autoimmune enteropathy), (iii) neoplastic syndromes involving the root of the mesentery (neuroendocrine and desmoid tumors—usually associated with familial adenomatous polyposis or Gardener's syndrome), and (iv) diffuse portomesenteric thrombosis with high risk of GI bleeding [61].

The causes of intestinal failure are different in adult versus pediatric patients. In infants, gastroschisis (21%), volvulus (18%), and necrotizing enterocolitis (12%) account for more than half of the cases. On the other hand, mesenteric vascular thrombosis (22%), Crohn's disease (13%), and trauma (13%) are the most frequent causes of intestinal failure in the adult population [62,63]. Based on data from the International Intestinal Transplant Registry, approximately 60% of the recipients receiving an intestinal transplant had an underlying diagnosis of short bowel syndrome [59]. The development of SBS depends not only on the length of bowel resected, but also on the location of the resection, on the presence or absence of the ileocecal valve, and on the presence or absence of the colon. As a rough guideline, most patients can tolerate resection of 50% of their intestine with subsequent adaptation, avoiding the need for long-term parenteral nutritional support. Loss of greater than 70% of the intestine (considered ultra short gut syndrome), however, usually necessitates some type of parenteral nutritional support. The development of TPN-induced liver failure is much more rapid in children when compared to adults. For these reasons pediatric patients should be considered early for intestinal transplantation before development of irreversible liver injury [64].

The pretransplant evaluation is not too different from that for other transplants. A clear understanding of the anatomy of the patient's GI tract is essential. An upper GI tract series and abdominal CT scan are always necessary in order to plan GI tract reconstruction during the transplant. Hepatic function should be evaluated carefully and a transjugular or percutaneous liver biopsy is often required. If there is evidence of significant liver dysfunction and cirrhosis, a combined liver-intestine or multivisceral transplant may be indicated [65]. Patients with thrombotic disorders need specific hematologic tests to define hypercoagulable states (such as protein C and S deficiency, prothrombin G20210 A and factor V Leiden mutation, and hyperhomocysteinemia). A full abdominal visceral angiography and a comprehensive evaluation of upper and lower central venous system is mandatory in high-risk patients and those with thrombotic disorders. Absolute contraindications such as malignancy, active infection, marked cardiopulmonary insufficiency must be ruled out [62,63,66].

Recently, there has been an increased interest in performing isolated intestine procedures in recipients with early liver failure as there is mounting evidence to suggest that TPN-associated liver disease may be reversed with successful isolated intestine transplant [67,68]. Therefore, early referral of such patients is warranted to see if attempts can be made to salvage the liver.

Surgical Procedure

The indication for transplant and the choice of organs to include in the composite graft are defined by the baseline disease, recipient's anatomy, associated disease (such as diabetes, exocrine pancreatic insufficiency, and renal failure), and functional quality of other abdominal organs. The three most common types of transplants involving the small intestine include isolated intestinal transplantation, combined liver–intestine transplant, and multivisceral transplants [61–63].

The isolated intestine is the graft of choice for patients with irreversible gut failure that is limited to the small bowel. The

vascular anastomoses are based on the superior mesenteric vessels. The outflow is usually achieved with the anastomosis of the superior mesenteric vein to the native superior mesenteric vein or splenic vein; however, in some cases a systemic drainage (inferior vena cava) is required. Systemic drainage will lead to certain metabolic abnormalities, but there is no good evidence to suggest that such abnormalities are of any obvious detriment to the recipient. In patients with combined pancreatic dysfunction (i.e., cystic fibrosis, type I diabetes and chronic pancreatitis) the inclusion of the pancreas should be considered. In living donation or in case of severe donor-to-recipient size mismatch (cadaveric adult to pediatric donation), a 200-cm length of the distal small bowel is used; inflow to the graft is via the ileocolic artery, and outflow via the ileocolic vein [61–63,69].

For a combined liver and intestinal transplant, the graft is usually procured intact with an aortic conduit, which contains both the celiac and superior mesenteric arteries. The common bile duct can be maintained intact in the hepatoduodenal ligament along with the first part of the duodenum and whole pancreas. Doing so avoids a biliary reconstruction in the recipient. A partial pancreatectomy, keeping a small rim of the head of the pancreas is also an alternative technique to avoid hilar dissection; however, this procedure has been abandoned by most centers, due to high risk of complications (i.e., pancreatitis and pancreatic fistulas). During the liver–small bowel transplant, the native stomach, duodenum, pancreas, and spleen are left intact and a portocaval shunt is always required for outflow reconstruction of the native organs [61–63].

The third type of transplant including the small bowel is the multivisceral transplant. In general, multivisceral grafts are those which contain a donor stomach, pancreas, and intestine. The common indications for multivisceral transplant include, but are not limited to, hollow visceral myopathy or neuropathy, pseudo-obstruction syndrome, extensive GI polyposis and total symptomatic splanchnic vascular thrombosis. The surgery encompasses the complete splanchnic evisceration and en bloc transplantation of stomach, duodenum, pancreas, liver, and small bowel (full multivisceral transplant). In some occasions, the right and transverse colon can also be included. In patients with preserved liver function, the native liver can be preserved (so called modified multivisceral transplant). In patients with established or impending renal failure, a renal graft (usually right kidney) can also be included in the multivisceral or liver–intestine allografts.

Several factors should be considered in appropriately matching the donor and recipient. Usually ABO-identical grafts are used; ABO nonidentical but compatible grafts are usually avoided because of the higher risk of graft-versus-host disease. Donors should usually be smaller than the recipients, as the latter usually have shrunken peritoneal cavities, and so a smaller graft may be more appropriate because of space constraints. Selective decontamination of the gut (amphotericin B, polymyxin B, and gentamicin) through a nasogastric tube should be attempted in all the donors. CMV enteritis can be a devastating problem in intestinal transplant recipients, and so, if possible, CMV seronegative recipients should receive organs from seronegative donors. Similar viral matching should be performed for EBV, if possible, because of the risk for PTLD [62,69–71].

The recipient operation varies, depending on the graft being implanted. The recipient's surgery is usually a complex procedure due to the presence of abdominal adhesions, stomas, gastrojejunostomies tubes, contracted abdominal cavity, and, in some cases, considerable portal hypertension (patients requiring combined allografts). Generally, arterial inflow to the graft is achieved using the recipient's infrarenal aorta to perform an end-to-side anastomosis (usually an interposition arterial graft is required). This technique is used for all the abovementioned grafts. The venous drainage is achieved either into the portal system or into the inferior vena cava. In full multivisceral or liver–intestine allografts, the venous drainage is established by piggy-back technique or by interpositioning the retrohepatic caval portion.

GI continuity can be achieved by a number of different methods. Commonly the proximal anastomosis of isolated intestine or liver–intestine is a side-to-side jejunojejunostomy. In multivisceral allografts (full or modified), the proximal anastomosis is performed between the stomach to the native esophagus or stomach stump. In multivisceral transplantation a pyloroplasty should be always performed to avoid delayed gastric emptying.

Gastrojejunostomy tubes are usually used permitting gastric decompression and enteral feeding in the early postoperative period. A Bishop–Koop enterostomy (chimney) or loop ileostomy are used to decompress the terminal ileum and to facilitate enteroscopies and biopsies, which is the only reliable method to monitor the allograft and diagnose acute rejection. Finally, the remaining recipient large intestine is anastomosed with the allograft roughly 20 cm proximal to the end ileostomy. Of note, cholecystectomy is performed in all the cases.

Postoperative Care

The early posttransplant care is, in many ways, similar to that of other transplant recipients. Initial care is usually in a critical care setting, so that fluid, electrolytes, and blood product replacement can be carefully monitored. Serial hemoglobin measurements are performed to look for any evidence of bleeding. Serum pH and lactate should also be monitored to look for evidence of intestinal ischemia or injury. In patients who received liver-intestine or multivisceral allografts, pancreatic enzymes and liver function tests should be assessed daily to track the organ functional status. Broad-spectrum antibiotics are routinely administered given the high risk for infectious complications. Routine prophylaxis should also be administered against CMV and EBV infection, especially in the seronegative recipient. Most centers usually use IV ganciclovir with or without the addition of CMV immunoglobulin. The gut decontaminant solution is given enterally, until the enteral feeding is started. Protozoal prophylaxis (i.e., *Pneumocystis* pneumonia) with trimethoprim–sulfamethoxazole should be started in the first week after transplant [62,63].

Immunosuppression should be initiated immediately after surgery. A number of different immunosuppressive protocols have been described. Most centers use lymphoid depleting agents, including Thymoglobulin or alemtuzumab for induction therapy, followed by a tacrolimus-based maintenance regimen [70,71].

Regardless of the protocol, intestinal transplants clearly have a high risk of rejection (incidence of 30% to 50% in the first 90 days after the transplant). It is very important to differentiate enteritis (mostly caused by *Clostridium difficile*, adenovirus, cytomegalovirus and calicivirus) from rejection, since both conditions may be characterized by diarrhea (or increased stoma output), abdominal pain, and low-grade fever. Therefore, careful evaluation of an intestinal biopsy by an experienced pathologist is always necessary. In addition to routine and regular endoscopy and biopsy, other noninvasive markers of intestinal rejection have been described. Recently studies have shown that several molecules, such as calprotectin and citrulline (measured in the stools and blood, respectively), are reliable markers of moderate and severe intestinal rejection [66]. Acute rejection episodes are often associated with infections. Rejection results in damage to the intestinal mucosa, leading to impaired mucosal barrier function and bacterial translocation. Therefore, advanced rejection can be very difficult to treat.

The switch from parenteral to enteral nutrition is gradual and usually occurs in the first 2 weeks after transplant. Antidiarrheic or prokinetic agents are used to modulate the stoma output after transplant, once rejection or enteritis is ruled out.

Short-term results have improved dramatically, mainly due to improvements in surgical technique and in immunosuppression [61,69,71]. Nonetheless, intestinal transplants are still associated with a high complication rate. Potential complications include enteric leaks with generalized peritonitis or localized intra-abdominal abscesses, graft thrombosis, respiratory infections, and life-threatening hemorrhage.

Infectious complications are, unfortunately, very common in intestinal transplant recipients. There are several factors that contribute to this. The intestinal graft itself is a significant source of bacteria, and any process which compromises containment of these bacteria (such as rejection or anastomotic leak) can lead to a systemic infection. Because of the higher risk of rejection, and the consequences associated with rejection, intestinal transplant recipients generally receive higher levels of immunosuppression compared with other organ recipients, usually in a greater immunosuppressed state. Bacteria can translocate from the graft directly into the peritoneal cavity itself, leading to bacterial peritonitis. Bacteria can also spread directly into the portal circulation, and subsequently disseminate to other sites. Besides bacterial infections, viral infections with CMV, EBV, or adenovirus are also more common in intestinal transplant recipients.

Outcomes

According to the UNOS Database, 1,785 intestinal transplants have been performed in the United States since 1990 (UNOS/OPTN, www.optn.transplant.hrsa.gov/, accessed August, 2009). Currently, only eight Medicare-approved centers in the United States perform intestinal/multivisceral transplant. However, 29 centers throughout the country are listed in the International Intestinal Transplant Registry as active small bowel transplant centers [59,60].

Over the past 15 years, there has been a remarkable improvement in short-term patient and graft survival. This is a result of combination of advances in surgical techniques, immunosuppressive strategies, and postoperative management. The 1-year graft and patient survival rates are now about 80%, with no significant difference between the different types of allografts. In spite of the significant improvement of short-term survival, the 5-year survival rate has remained stable at approximately 60%, and the presence of the liver in the composite allograft (liver–intestine and full multivisceral transplants) is associated with a significant improvement in the long-term survival. The most common causes of graft loss and patient death are quite similar and include rejection, technical failure, and infection/sepsis. Other causes of graft loss and death are post-transplant lymphoproliferative disorders (lymphomas), graft-versus-host disease, and pancreatitis (in combined allografts) [61,70,71].

SUMMARY

Care of liver and intestinal transplant recipients, before, during, and after surgery is a significant challenge. The potential is great for an array of complicated medical and surgical problems. Despite dramatic advances in the field, these procedures remain major undertakings with the possibility of complications affecting every major organ system. A systematic approach is necessary to prevent, minimize, and manage these complications. Intensive medical care in an ICU setting may be necessary even pretransplant, especially in patients with fulminant hepatic failure or severely decompensated chronic liver disease. Optimizing the overall medical status of the transplant candidates with chronic liver failure is essential to minimize the likelihood of postoperative problems. Immediately posttransplant, intensive monitoring—with diligent attention to all organ systems—is necessary to ensure a successful outcome. A thorough knowledge of potential complications is required to allow for rapid diagnosis and appropriate treatment.

Improvements in the care of these patients during the critical perioperative period, along with better immunosuppressive regimens, have allowed for remarkable advances (Table 187.4). A liver transplant is the only real treatment of choice for patients with acute and chronic end-stage liver disease. Most centers now report 1-year patient survival rates of about 85% and 5-year survival rates of more than 70%. Intestinal transplants are becoming an increasingly used option for patients with intestinal failure. As results continue to improve, this will become an alternative option to long-term maintenance therapy with TPN. For both liver and intestinal transplants, the future will likely see further improvements in results (with refinements in surgical and preservation techniques and with newer drugs to treat rejection and infections). Care of these patients in the critical perioperative period, however, will remain a crucial aspect of ensuring a successful outcome.

TABLE 187.4

MAJOR ADVANCES OR CHANGES IN THE LIVER TRANSPLANTATION FIELD OVER THE LAST 10 YEARS

Topic	Change	Reference
Allocation system	MELD/PELD utilized widely in the United States with evidence-based analysis showing it to improve patient survival	[10]
Indications for transplant	Extended tumor criteria outside of Milan criteria with equivalent results—for example, UCSF criteria	[16,17]
Surgical technique	Growth in adult-to-adult living donor transplant Donor morbidity for above estimated at 30%–35%	[28,29]
Increasing the donor pool	Increasing use of marginal donors nonheart beating donors, and split livers to expand the donor pool	[7,33,34]
Viral recurrence	Effective prophylaxis regimens to significantly decrease the risk of hepatitis B recurrence after transplant Hepatitis C recurrence becoming an increasing problem	[57,58]

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CHAPTER 188 ■ HEMATOPOIETIC CELL TRANSPLANTATION

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GENERAL PRINCIPLES

Hematopoietic cell transplantation (HCT) typically is performed in patients with life-threatening disorders of the hematopoietic system. The procedure has considerable risks of transplant-related morbidity and mortality with a substantial proportion of patients requiring intensive medical care [1,2] (Fig. 188.1). Thus, knowledge of the basic principles of the transplant procedure and an understanding of potential complications including their differential diagnosis are important for improving the outcome of critically ill patients after transplantation.

HCT is potentially curative treatment for diseases including leukemia, lymphoma, myelodysplasia, multiple myeloma, aplastic anemia, hemoglobinopathies, and congenital immune deficiencies. In selected cases, HCT may also have a role in the treatment of solid tumors such as germ cell tumors, renal cell cancer, and breast cancer, and as a type of immunosuppression for patients with life-threatening autoimmune diseases (Table 188.1). In preparation for HCT, high-dose chemotherapy alone, or combined with irradiation therapy, is used to eradicate the underlying disease and to induce transient immunosuppression in the recipient to prevent graft rejection, a possible complication mediated by immunologic host-versus-graft reactions after allogeneic HCT. High-dose chemoradiation is followed by intravenous infusion of the graft, which contains hematopoietic stem cells (HSCs) that home to the bone marrow and reconstitute the hematopoietic system of the patient. In contrast to autologous HCT, allogeneic HCT requires prophylactic immunosuppressive therapy after transplant to prevent or mitigate graft-versus-host disease (GVHD), an inflammatory syndrome that primarily affects the skin, gastrointestinal (GI) tract, and liver.

Classification

HCT can be categorized according to the source of stem cells, the type of donor, or the intensity of the preparative regimen. The type of HCT used in an individual patient is a complex decision based on the patient's age, diagnosis, disease stage, prior treatments, donor availability, and presence of comorbidities.

Stem Cell Source

HSCs capable of reconstituting hematopoiesis in recipients given myeloablative therapy can be obtained from bone marrow, peripheral blood, or umbilical cord blood (UCB). The stem cell products obtained from each of these sources are characterized by distinct kinetics of engraftment and recovery of immune function after transplantation. These features may affect the risks of developing infectious complications and GVHD during the posttransplant period.

Bone Marrow. Bone marrow was historically the most common source of stem cells for HCT but is now used very infrequently for autologous HCT. Bone marrow is harvested from the iliac crest under general anesthesia, from appropriate volunteer donors. Engraftment after bone marrow transplant is evidenced by rising neutrophil and platelet counts and occurs between 3 and 4 weeks after transplant.

"Mobilized" Peripheral Blood. Growth factor–mobilized peripheral blood stem cells (PBSC) are the predominant source of HSC for allogeneic HCT in adults and are almost always used as HSC rescue for autologous HCT [3]. PBSCs are recognized on the basis of their expression of the CD34 surface marker and can be collected from the blood by a semiautomated procedure called leukapheresis. To promote peripheral blood mobilization of PBSC for autologous HCT, patients typically receive chemotherapy followed by administration of G-CSF, which has the benefit of chemotherapy-mediated tumor debulking prior to stem cell collection [4]. For allogeneic HCT, PBSCs are mobilized from healthy donors using growth factor alone.

Engraftment after PBSC transplantation occurs approximately 1 week earlier compared with bone marrow transplantation, which is likely related to the greater proliferative potential of stem and progenitor cells in PBSC. PBSC allografts contain approximately 10 times more T cells than marrow, which influences the development of GVHD, graft rejection, and rate of relapse for malignancies after HCT [5]. Randomized studies of allografts donated from HLA-matched siblings have shown a higher risk for relapse and lower risk for chronic GVHD among recipients of marrow compared with PBSC [3,6].

Umbilical Cord Blood. UCB contains HSC sufficient for reconstitution of hematopoiesis, which can be collected from the placenta and umbilical cord immediately after delivery of a baby. UCB banking has increased the likelihood of donor availability for patients with rare HLA haplotypes. T cells contained in UCB are immunologically naive, which allows for less stringent HLA matching between donor and recipient. The number of HSC contained in a typical UCB unit is several orders of

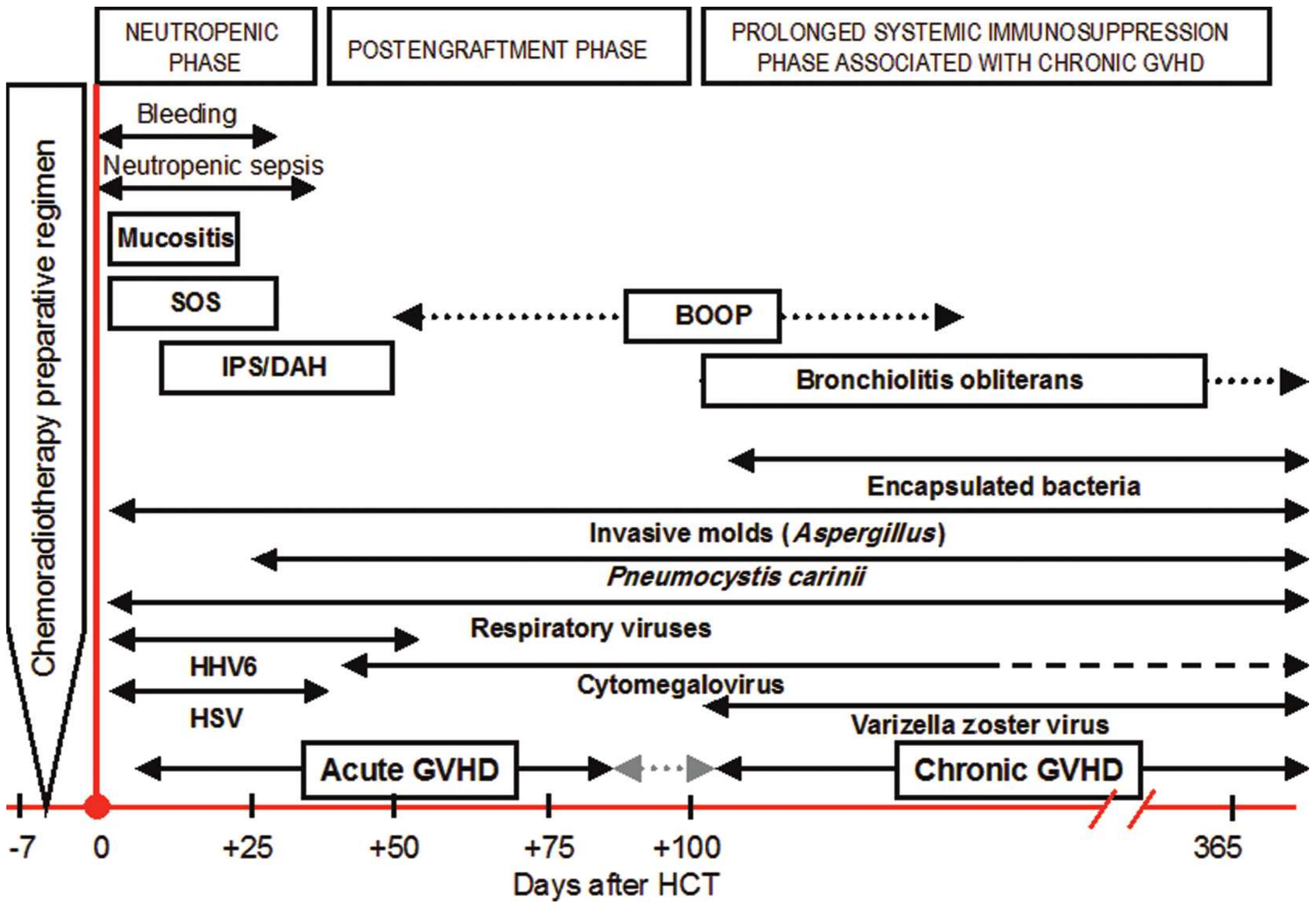

FIGURE 188.1. Complications after myeloablative allogeneic hematopoietic cell transplantation. BOOP, bronchiolitis obliterans with organizing pneumonia; DAH, diffuse alveolar hemorrhage; GVHD, graft-versus-host disease; HHV6, human herpes virus 6; HSV, herpes simplex virus; IPS, idiopathic pneumonia syndrome; SOS, sinusoidal obstruction syndrome.

TABLE 188.1

INDICATIONS FOR ALLOGENEIC OR AUTOLOGOUS TRANSPLANTS

Allogeneic	Autologous
High-risk acute leukemia Acute myeloid leukemia Acute lymphoblastic leukemia	High-risk lymphoma Non-Hodgkin's lymphoma Hodgkin's lymphoma
Chronic leukemia Chronic myeloid leukemia Chronic lymphocytic leukemia	Multiple myeloma
Juvenile myelomonocytic leukemia	Solid tumors Neuroblastoma Poor-risk breast cancer Poor-risk sarcoma
Chronic myelomonocytic leukemia	Investigational Other poor-prognosis tumors Refractory autoimmune disorders
Myelodysplastic syndromes	
Bone marrow failure syndromes Severe aplastic anemia	
Severe immunodeficiency syndromes	
Inborn errors of metabolism	
Hemoglobinopathies Thalassemia major Symptomatic sickle cell disease	

magnitude lower compared with typical bone marrow or PBSC harvests. The smaller number of HSC may result in delayed engraftment, increased risk for graft rejection, and infection [7,8]. Recent studies have shown that infusion of two UCB units increases the total number of HSC, which seems to decrease the risk of graft rejection, thus giving adults as well as children the option of UCB transplantation [9].

Donor Type

Autologous. Transplantation of HSC donated by the patient is termed autologous HCT. Most commonly, autologous PBSC are cryopreserved and then thawed and reinfused once the high-dose preparative therapy has been completed. High-dose chemoradiation is given to kill tumor cells that may not be susceptible to conventional-dose cytotoxic therapy. The success of the autologous transplant procedures relies exclusively on the tumor-eradicating potential of the preparative regimen [10]. The effect the conditioning regimen has on extrahematopoietic tissues determines the dose-limiting toxicity of the procedure. Relapse after autologous HCT may occur from tumor cells that have survived the conditioning therapy or from those that contaminated the graft, although the former mechanism appears to be more important.

Syngeneic. Transplantation of HSCs donated from identical (monozygotic) twins is termed syngeneic HCT. When there is no genetic disparity between donor and recipient, the biology of the transplant is similar to autologous HCT. Compared with allogeneic HCT from HLA-matched related or unrelated donors, relapse rates are higher after syngeneic HCT, which has been attributed to the absence of malignancy-eradicating graft-versus-host reactions.

Allogeneic. Transplantation of HSCs cells donated by another individual is termed allogeneic HCT. Allogeneic HCT requires

availability of an HLA-compatible related or unrelated donor. Because of the inheritance pattern of HLA haplotypes, the statistical likelihood of two siblings being genotypically HLA identical is 25%. Donor-recipient HLA genotypic identity is associated with the lowest risks for immunologically mediated complications such as graft rejection and GVHD [11]. For approximately 70% of patients who do not have an HLA-identical sibling donor, a search for a suitable unrelated donor can be considered. HCT from HLA-matched unrelated donors, however, has traditionally been associated with higher risks of transplant-related morbidity and mortality compared with HCT from HLA-identical related donors. Use of unrelated donors who are matched using molecular HLA typing methods can improve outcomes considerably, and, for some diseases, survival of patients with unrelated grafts has approached that with HLA-identical sibling grafts [12,13].

The worldwide development of donor registries has increased the number of available HLA-matched unrelated donors and umbilical cord blood units for patients without suitable related donors. Another alternative source of HSC is a haploidentical relative, such as a parent, defined by the inheritance of one identical haplotype and mismatching of one or more HLA loci with the noninherited haplotype. Over the past decade, technological advances have improved the outcome for recipients of HLA-disparate grafts. When more than a single HLA antigen disparity is present, depletion of T cells from the graft is necessary to prevent life-threatening GVHD. Depletion of T cells from the marrow may be accomplished ex vivo by using immunologic or physical methods to target T cells for removal. Because T cells play an important role in establishment of the graft, early immune reconstitution, and tumor control, T-cell depletion has been associated with higher rates of graft failure, opportunistic infections, and relapse. Strategies to selectively deplete alloreactive T cells remain an active area of research.

Intensity of the Preparative Regimen

Myeloablative

In myeloablative HCT, the preparative regimen ablates the hematopoietic system of the patient and leads to transient but profound myelosuppression with pancytopenia. The transplanted hematopoietic cells reconstitute the ablated hematopoietic system in the recipient. High-dose chemotherapy regimens, with or without doses of total body irradiation (TBI) that exceed 6 Gy, combine different drug combinations that have nonadditive toxicities with radiation. The aim of high-dose therapy is to overcome the genetic heterogeneity of tumors by employing agents with different mechanisms of action. Although the myeloablative regimens used for autologous HCT typically consist of drugs that provide maximum tumor eradication with tolerable toxicity to the patient, regimens used for allogeneic HCT also must provide sufficient recipient immunosuppression to prevent graft rejection. Myeloablative preparative regimens are associated with substantial risks of transplant-related toxicity and mortality, particularly among older or medically ill patients [14].

Nonmyeloablative

Nonmyeloablative preparative regimens for allogeneic HCT are mainly immunosuppressive and aimed at preventing graft rejection. The underlying malignancy is eliminated through the ensuing immunologic graft-versus-tumor effects, provided the tumor expresses antigens that make it a target for immune attack. Compared with myeloablative allogeneic HCT, the extrahematopoietic toxicity from nonmyeloablative preparative regimens is considerably milder, an important consideration for older patients or those with comorbidities [15,16]. Typical post-HCT complications such as GVHD and infections, however, are not prevented by nonmyeloablative conditioning but may have a delayed onset.

Epidemiology

Current estimates of annual numbers of HCT are 45,000 to 50,000 worldwide. During 2006, 16,000 transplants were registered with the Center for International Blood and Marrow Transplant Research (CIBMTR), of which one-half were allogeneic. Allogeneic HCT is most commonly performed in adults using PBSC grafts. In contrast, children now predominantly receive cord blood or marrow grafts (NMDP Web site: http://www.marrow.org/). PBSC is less used in children because of the difficulties harvesting PBSC from young children and because of the increased risk of chronic GVHD.

Risk Factors for Transplant-Related Morbidity and Mortality

The likelihood of developing transplant-related complications depends on patient's age, the intensity of the preparative regimen, the type and stage of the underlying disease, and the presence of comorbidities. Prognosis is most heavily influenced by the underlying disorder. Patients with chronic malignancies and nonmalignant disorders, such as aplastic anemia, have a higher likelihood of survival compared to those with aggressive malignancies, who have a greater tendency to relapse following HCT. Mortality caused by the transplant procedure, and not from disease relapse, termed transplant-related mortality, ranges from 15% to 40% for allogeneic HCT recipients compared to 5% to 10% for autologous HCT recipients. HLA disparity between donor and recipient increases the risk of transplant-related mortality owing to the greater likelihood of developing GVHD and graft rejection. The risk for mortality increases significantly with age, although improvements in supportive care and donor selection and the introduction of nonmyeloablative preparative regimens have increased the proportion of patients older than 60 years who benefit from allogeneic HCT. Recent studies have demonstrated that pretransplant assessment of comorbidities using simple but transplant-specific comorbidity scoring systems has improved the ability to predict subsequent transplant-related mortality and survival [14,17].

TRANSPLANT-RELATED COMPLICATIONS

Transplanted-related complications include infections, regimen-related toxicity (RRT), and complications associated with alloreactivity. More intense conditioning regimens and higher degrees of donor-recipient HLA disparity are associated with greater risk for infection. Regimen-related toxicities include profound cytopenias and organ damage that follow myeloablative conditioning. The complications seen after allogeneic HCT that may occur irrespective of the intensity of the conditioning regimen include rejection, GVHD, and hemolysis.

Regimen-Related Pancytopenia

Reconstitution of hematopoiesis after HCT occurs in an orderly pattern; in general, neutrophil recovery occurs first, followed by recovery of platelets and red blood cells. The tempo of hematopoietic reconstitution varies according to the type

of HSC product, being earlier after PBSC grafts and later after UCB grafts, compared with marrow grafts. Transfusions of platelets and red blood cells often are needed until there is marrow recovery. Transfusion of red blood cells should be determined by the clinical condition of the patient, including hemodynamic stability and presence of active hemorrhage. Red blood cell transfusions generally are indicated when the hemoglobin falls below 8 g per dL. Platelet transfusions are indicated when the platelet count falls below 10,000 cells per μL to minimize the risk for spontaneous bleeding [18,19]. Transfusions thresholds should be increased before invasive procedures or in patients with bleeding to a level appropriate for any other intensive care unit (ICU) patient [18]. Platelet consumption may be increased in patients with fever, disseminated intravascular coagulation (DIC), or splenomegaly. Patients who have become alloimmunized to platelet antigens demonstrate poor response to platelet transfusions and may achieve higher platelet counts by limiting the number of donor exposures, controlling fever or DIC, using platelet products that are less than 48 hours old, or use of nonpooled (single-donor) or HLA-matched platelets [20,21].

Precautions should be taken in preparation of blood products for transfusion into HCT patients because passenger lymphocytes pose a risk for generating GVHD and latent viruses may be transferred through leukocytes. Except for the stem cell graft, all other components should be irradiated at a dose of 1,500 to 3,000 cGy to inactivate or eliminate contaminating lymphocytes. Depletion of leukocytes or use of blood components that test seronegative for cytomegalovirus (CMV) is effective for prevention of CMV transmission to CMV-seronegative recipients [21]. Removal of white blood cells from platelet and red blood cell products also decreases the risk for alloimmunization of the patient [22].

Regimen-Related Toxicity

High-dose cytotoxic chemotherapy with or without doses of TBI exceeding 6 Gy may severely disrupt mucosal integrity and has the potential to cause RRT in the skin, GI tract, liver, bladder, lung, heart, kidney, and nervous system. RRT occurs predominantly within the first 3 to 4 weeks after conditioning [23] and is more common after myeloablative than nonmyeloablative conditioning. RRT increases the risk for opportunistic infection, which is already high because of concomitant profound immunosuppression and regimen-related cytopenias. This section will focus on the noninfectious complications of individual organs specifically attributable to conditioning toxicity. Opportunistic infection or, after allografting, GVHD must strongly be considered as etiologies for organ dysfunction in the differential diagnosis of RRT. These alternative diagnoses are covered elsewhere under the appropriate subsection.

Skin

Generalized skin erythema is common after doses of TBI exceeding 12 Gy but is self-limiting and rarely associated with skin breakdown. Regimens that contain cytosine arabinoside (Ara-C), thiotepa, busulfan, etoposide, and carmustine may also cause erythema. Hyperpigmentation typically follows the inflammatory dermatitis, with skin folds often being particularly noticeable. Skin biopsies during the first 3 weeks after transplant often show nonspecific inflammatory changes irrespective of cause, making them frequently unhelpful in distinguishing between RRT, drug allergies, or acute GVHD [24].

Gastrointestinal Tract

Mucositis. Most patients who receive high-dose conditioning regimens develop mucositis. Symptoms include inflammation, desquamation, and edema of the oral and pharyngeal epithelial tissue that typically presents within the first several days after HCT and usually resolves by the third week. Anorexia, nausea, or other intestinal symptoms that persist after day 21 are more likely to be caused by GVHD or infection. Severe mucositis places patients at risk for aspiration and occasionally airway compromise, indicating the need for endotracheal intubation. Damage to the mucosa of the lower GI tract results in secretory diarrhea, cramping abdominal pain, and anorexia, and it facilitates translocation of intestinal bacteria with sepsis [23,25].

Mucositis is treated supportively with total parenteral nutrition, administration of intravenous fluids, and intravenous narcotics for pain control. It is important to recognize an iatrogenic narcotic bowel syndrome, characterized by abdominal pain and bowel dilatation, which occasionally may be a side effect of efforts to control painful symptoms of mucositis or sinusoidal-obstruction syndrome [26].

Acute Upper Esophageal Bleeding. The combination of mucositis, thrombocytopenia, and severe retching may result in a Mallory–Weiss tear, or esophageal hematoma [27]. The latter condition may have associated symptoms of dysphagia and retrosternal pain, and can be diagnosed by computed tomography (CT) scan. These conditions are treated supportively with transfusions to maintain platelet counts of greater than 50,000 per μL and optimal management of nausea and vomiting.

Liver

Sinusoidal Obstruction Syndrome. Sinusoidal obstruction syndrome (SOS; formerly referred to as veno-occlusive disease) develops in 10% to 60% of patients and is a clinical diagnosis based on the triad of tender hepatomegaly, jaundice, and unexplained weight gain usually within 30 days after HCT and in the absence of other explanations for these symptoms and signs [28,29]. It is more likely to be severe in patients with cirrhosis or fibrosis of the liver, or those with a history of hepatitis or liver irradiation (greater than 12 Gy), or chemotherapy-induced SOS [29,30].

Elevations of total serum bilirubin and serum transaminases are sensitive but nonspecific markers for SOS, and urinary sodium levels are typically low. A hepatobiliary ultrasound may show hepatomegaly, ascites, and dilatation of the hepatic vein or biliary system [31]. Doppler ultrasonography may show attenuation, or diagnostic, reversal of hepatic venous flow, but absence of this pattern does not exclude SOS [32]. If the diagnosis remains unclear, a transvenous liver biopsy may be helpful, and simultaneous measurement of hepatic venous pressure showing a gradient of greater than 10 mm Hg is highly specific for SOS [33].

Other causes of jaundice after HCT seldom lead to renal sodium avidity, rapid weight gain, or hepatomegaly. Cyclosporine, methotrexate, and total parenteral nutrition are iatrogenic causes of hyperbilirubinemia, although rarely cause levels greater than 4 mg per dL [34]. Combinations of illnesses that may mimic SOS are cholangitis lenta (cholestatic effects of endotoxin [35], especially when combined with renal insufficiency); cholestatic liver disease with hemolysis and congestive heart failure; GVHD and sepsis syndrome.

Once SOS is established, mathematical models can be used to predict prognosis, based on rates of increase in serum bilirubin and weight according to the elapsed time after transplantation [29,36]. The treatment for the 70% to 85% of patients who are predicted to have a mild or moderate course is largely supportive, with attention to management of sodium and water balance to avoid fluid overload [29]. Diuretics must be used judiciously to avoid depletion of intravascular volume and renal

hypoperfusion. Paracentesis is indicated if the degree of ascites threatens respiratory function. There is no universally effective therapy for severe SOS. However, multiple studies, including a recent large international multicenter phase II clinical trial, have demonstrated 30% to 60% complete remission rates with defibrotide, even among patients with severe SOS [37]. There is no support for insertion of peritoneovenous shunts and limited support for use of portosystemic shunts to reduce ascites [38]. Liver transplantation has been successful in a small number of patients [39].

Lung

Pulmonary complications occur in 40% to 60% of patients after HCT [40,41]. Noninfectious pulmonary problems that may occur within 30 days from the transplant include idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage, pulmonary edema [42] due to excessive sodium and fluid administration or associated with SOS, or acute cardiomyopathy induced by cyclophosphamide, and sepsis with adult respiratory distress syndrome (ARDS) [43]. These complications occur more frequently in older patients, those who receive higher-dose conditioning regimens, and those with allogeneic donors, particularly HLA-disparate donors [44]. Although the incidence of life-threatening pulmonary infections has decreased over the past decade due to the introduction of routine antimicrobial prophylaxis, pulmonary complications continue to be a leading cause of death.

Idiopathic Pneumonia Syndrome. IPS is defined as a noninfectious inflammatory lung process that may be triggered by TBI and chemotherapies such as carmustine or busulfan. IPS has been reported in 5% to 10% of patients and occurs with a median onset of 2 to 3 weeks after myeloablative HCT [44,45]. Contributing factors to IPS lung injury may be release of inflammatory cytokines due to alloreactivity or sepsis. The clinical symptoms cannot be distinguished from infection, and may include fever, nonproductive cough, and tachypnea. Hemoptysis is infrequent and more likely related to indicate invasive fungal disease or diffuse alveolar hemorrhage. Radiographic imaging shows diffuse interstitial or multifocal intra-alveolar infiltrates. Arterial blood gases show hypoxemia and the alveolar–arterial oxygen gradient is increased. In the occasional patient who is not too ill to attempt lung function studies, a new restrictive pattern or a reduced diffusing capacity is characteristic. Measurements of pulmonary artery occlusion pressure or echocardiography may be useful to rule out cardiogenic pulmonary edema. Bronchoalveolar lavage or lung biopsy is necessary to exclude bacterial, fungal, or viral infection because *IPS is a diagnosis of exclusion*. Multifocal bronchiolitis obliterans with organizing pneumonia (BOOP) may mimic late-onset IPS and has been more commonly associated with chronic GVHD.

Management of IPS is mainly supportive, including judicious diuresis to decrease pulmonary edema, transfusions of blood components to reverse bleeding diathesis, support of oxygenation, and administration of antibiotics to prevent superinfection with mold and bacteria, particularly in patients receiving high-dose glucocorticoids. Effective therapy for idiopathic pneumonia has not been demonstrated. High-dose glucocorticoids (1 to 2 mg per kg) have been reported to have an adjunctive role in treatment of diffuse alveolar hemorrhage or idiopathic pneumonia, but their efficacy has not been validated in controlled studies [46]. In a recent study of 15 patients who had IPS after allogeneic HCT, combination treatment with soluble tumor necrosis factor receptor (etanercept) and glucocorticoids resulted in an encouraging day-28 survival rate of 73% [47]. More than half of the patients included in this study had required mechanical ventilation at therapy onset. Long-term survival, however, did not appear to be superior compared with historic controls.

The mortality associated with IPS after myeloablative HCT is 50% to 70% [45,48]. Aggressive management, including initiation of mechanical ventilation to identify and treat reversible causes of respiratory failure, is a reasonable approach for most HCT recipients with diffuse or multifocal pulmonary infiltrates. When hemodynamic instability or sustained hepatic and renal failure develop, survival is extremely unlikely. Withdrawal of mechanical ventilation may be appropriate in specific situations.

Acute Respiratory Distress Syndrome. An ARDS-like syndrome also has been described as a presenting feature of acute GVHD, typically early-onset (hyperacute) GVHD. ARDS has an extremely high mortality rate in the transplant population; recovery depends on aggressive treatment of associated infections and support of respiratory and cardiac function [49,50]. The diagnosis of ARDS often is complicated by presence of other illnesses, such as SOS, hemorrhage, or disseminated intravascular hemolysis, which can cause difficulties in fluid management and indicate the need for pulmonary artery catheterization.

Diffuse Alveolar Hemorrhage. Diffuse alveolar hemorrhage may be a manifestation of diffuse alveolar damage. However, the erosion of blood vessels by fungal organisms always needs to be considered [51]. Hemorrhage occurs more frequently in older patients and those with malignancy, severe mucositis, or renal failure [52]. Bloody bronchoalveolar lavage (BAL) fluid with hemosiderin-laden macrophages is characteristic of diffuse alveolar hemorrhage.

Heart

Cardiac complications occur in 5% to 10% of patients after HCT, but death from cardiac failure is uncommon [53,54]. Cardiac injury with hemorrhagic myocardial necrosis is a rare but known adverse effect of high-dose cyclophosphamide, one of the most commonly used chemotherapy agents in conditioning regimens. Acute cardiac failure due to cyclophosphamide has a case mortality rate exceeding 50%. Risk factors for cyclophosphamide cardiotoxicity include use of doses equal to or greater than 120 mg per kg, an underlying diagnosis of lymphoma, prior radiation to the mediastinum or left chest wall, older age, and prior abnormal cardiac ejection fraction [54,55]. Patients who had prior cumulative anthracycline exposures of 550 mg per m^2 doxorubicin equivalents are at an increased risk for developing heart failure. Signs and symptoms of congestive heart failure may occur within a few days of receiving cyclophosphamide, while anthracycline-related cardiomyopathy may have a delayed onset. The electrocardiogram (ECG) may show voltage loss or arrhythmia, and echocardiography may reveal systolic dysfunction, pericardial effusion or tamponade [56]. Older age and a history of abnormal ejection fraction are other factors that predispose to cardiac toxicity [54]. Management includes attention to fluid and sodium balance, afterload reduction, and inotropes.

Kidney and Bladder

Acute Renal Failure. Acute renal failure (ARF), defined by doubling of baseline serum creatinine, occurs in 30% to 50% of all patients during the first 100 days after HCT, and most often during the first 10 to 30 days [57,58]. Occasionally, ARF develops during conditioning or infusion of HSC, as a consequence of tumor or red-cell lysis. ARF occurs most frequently in the setting of SOS and is characterized by low urinary sodium concentration and high blood urea nitrogen to creatinine ratio, similar to the hepatorenal syndrome. Renal hypoperfusion, caused by

acute hemorrhage, sepsis, or high-volume diarrhea, may result in ARF. Nephrotoxic drugs like cyclosporine, tacrolimus, all amphotericin products, and aminoglycosides frequently cause renal insufficiency.

Thrombotic microangiopathy (TMA), endothelial damage caused by chemoradiotherapy, cyclosporine, tacrolimus, or sirolimus, occurs in 5% to 20% of patients, more frequently in allograft recipients [59]. The hallmark of thrombotic microangiopathy is red blood cell (RBC) fragmentation (schistocytes) associated with increased RBC turnover (increased reticulocytes; elevations of serum lactate dehydrogenase and indirect bilirubin) without evidence for immune-mediated hemolysis or disseminated intravascular coagulation. The syndrome ranges from subclinical hemolysis to a life-threatening hemolytic syndrome, the latter being seen more frequently when sirolimus therapy is combined with cyclosporine or tacrolimus (calcineurin inhibitors, CNIs) and immediately following conditioning with busulfan and cyclophosphamide. High-therapeutic or supratherapeutic serum levels of CNIs or sirolimus are more prone to be associated with TMA [60]. Management involves careful assessment of volume status and discontinuation or adjustment of the drug levels of the offending agent(s). The use of plasma exchange has been associated with high mortality rates in most series [61] with recent exceptions [62], and may be skewed by selection bias because only the sickest patients are likely to receive the treatment. For this reason, determination of any survival benefit attributable to plasma exchange in the absence of a controlled study is impossible.

Hypertension. Hypertension develops in approximately 60% of patients after HCT, more often in patients given CNIs for GVHD prophylaxis. Glucocorticoid therapy also contributes to the development of hypertension. Uncontrolled hypertension may lead to fatal intracerebral bleeding in thrombocytopenic patients. Therefore, hypertension should be anticipated and controlled medically. Most patients respond to conventional antihypertensive therapy, such as a calcium channel blocker, angiotensin-converting enzyme inhibitor, or beta-blocker. Correction of hypomagnesemia, which often confounds CNI therapy, may improve control of hypertension [63].

Hemorrhagic Cystitis. High-dose cyclophosphamide is commonly used for conditioning, and one of its toxic metabolites, acrolein, accumulates in the urine and may cause a hemorrhagic chemical cystitis during the conditioning regimen or later after HCT [64,65]. Measures to prevent hemorrhagic cystitis include aggressive fluid hydration to increase urine volume that dilutes and minimizes contact of acrolein with the mucosa, and administration of the drug mesna, which provides free thiol groups to detoxify acrolein. Viral infections, particularly adenovirus and BK virus, also have been implicated in the development of hemorrhagic cystitis [66] and the diagnosis is established by viral culture or polymerase chain reaction (PCR) test of a urine sample [66]. Unless there is evidence of disseminated infection, viral cystitis is managed with supportive therapy, including aggressive hydration and platelet transfusions. Intravesicular infusions of ε-aminocaproic acid or prostaglandins have been reported to improve outcome of severe hemorrhagic cystitis [67]. Severe hemorrhagic cystitis caused by BK virus that proves refractory to supportive therapy may respond to therapy with cidofovir [68].

Central Nervous System

Noninfectious complications include cerebrovascular events and encephalopathies due to metabolic, toxic, and immune-mediated causes. Focal symptoms are more indicative of infectious or cerebrovascular mechanisms, while diffuse symptoms such as delirium or coma may have metabolic causes. Fever is not necessarily associated with central nervous system (CNS) infections. Infection should be considered as the cause of any neurologic symptom and should prompt evaluation, including obtaining CT or magnetic resonance imaging (MRI) scans of the head and a sample of cerebrospinal fluid for appropriate cultures, cytochemistry stains, and PCR tests should be undertaken.

Cerebrovascular Events. Thrombocytopenia poses a risk for intracranial hemorrhage, which usually presents as abrupt onset of focal neurologic deficit or mental status changes [69]. Patients with sickle cell disease have a predisposition to CNS hemorrhage after HCT and should be managed carefully by ensuring sufficient platelet and magnesium levels and strict control of hypertension [70]. Ischemic stroke is an unusual complication after HCT but has been reported in patients with *Aspergillus* infections, hypercoagulable states, or TMA [59,71].

Toxic Encephalopathies. Conditioning with high-dose busulfan or carmustine may cause encephalopathy and seizure prophylaxis with phenytoin is usual. High-dose cytarabine may cause cerebellar dysfunction, encephalopathy, and seizures. High-dose cyclophosphamide can be associated with the syndrome of inappropriate antidiuretic hormone (SIADH), rarely causing acute decline in the serum sodium that may prompt seizures. Fludarabine, used frequently in nonmyeloablative conditioning, may cause an encephalopathy.

A rare syndrome of encephalopathy and hyperammonemia without other chemical evidence of liver failure has been reported after HCT [72]. Contributing factors may include hypercatabolism induced by conditioning, glucocorticoids, or sepsis, and high nitrogen loads associated with parenteral nutrition or intestinal hemorrhage. The syndrome is difficult to reverse and has a high mortality rate. Treatment involves hemodialysis and administration of ammonia-trapping agents, such as sodium benzoate or sodium phenylacetate.

Related to a tendency to accumulate in nervous tissues due to their lipophilic characteristics, CNIs can cause a range of neurologic toxicities [73]. Tremor develops in most patients. Seizures have been reported in up to 6% of patients and may present in association with headaches, tremor, or visual disturbances [74]. Seizures should be managed with anticonvulsant therapy and cessation of the drug. When CNIs are essential for management of GVHD, substitution of one agent for the other, or reinstitution of the offending agent at a lower dose, may be feasible [75]. A unique and usually reversible syndrome of cortical blindness has been reported as a complication of cyclosporine treatment; hypertension and hypomagnesemia are thought to be predisposing factors [76]. Toxicity due to calcineurin inhibitor therapy may occur with "therapeutic" drug levels, and clinical suspicion is often confirmed by MRI scans that show multifocal areas of signal hyperintensity on T2 (time for 63% of transverse relaxation) and fluid-attenuated inversion recovery (FLAIR) sequences, most often in the occipital lobe white matter.

Glucocorticoid therapy may be associated with psychosis, mania, or delirium in a dose-dependent fashion. Seizures or altered sensorium may be associated with the use of sedative-hypnotic drugs and have been reported as adverse side effects of many of the commonly used antibiotics and antiviral agents. Metabolic encephalopathy may be associated with Gram-negative sepsis, hypoxic encephalopathy with IPS, and hepatic encephalopathy due to SOS or GVHD.

Treatment of metabolic encephalopathies should be directed at the underlying problem, and offending drugs have to be discontinued. In patients with CNI neurotoxicity, temporary discontinuation of the CNI and the restarting at a lower dose is usually successful. Short-term phenytoin for seizure prophylaxis may be indicated.

Infection

Conditioning regimens and GVHD severely impair host defense mechanisms, and the process of immune reconstitution necessarily requires many months for completion. Together these factors place patients at high risk for acquisition of severe infections. Proper medical care of patients after HCT includes measures to monitor and prevent infection, as it is a leading cause of death.

Prevention of infection is of vital importance to the success of HCT procedures. Hospitalized patients should be housed in single rooms that have positive-pressure airflow and ventilation systems with rapid air exchange and high-efficiency particulate air filtration [77]. Strict visitation, hand washing, and isolation policies should be instituted to prevent introduction or spread of communicable disease. A daily program of skin and oral care should include bathing all skin surfaces with mild soap, brushing teeth with a soft brush, frequent rinsing of the oral cavity with saline, and good perineal hygiene. The diet should exclude foods known to contain bacteria or fungi, and patients should avoid exposure to dried or fresh plants or flowers. Caregivers should be trained in the proper handling of central venous catheters.

Immunologic reconstitution after HCT can broadly be categorized into three phases, which are characterized by a spectrum of opportunistic infections. Advances in management of antimicrobial prevention of opportunistic infections after HCT are outlined in Table 188.2.

Before Engraftment Period

The period before engraftment (less than 30 days posttransplant) is characterized by neutropenia and oral and gastrointestinal mucosal damage. The most common infections are bacterial and fungal. The use of indwelling central venous catheters

TABLE 188.2

ADVANCES IN PREVENTION OF OPPORTUNISTIC INFECTIONS AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Infection	Recommendations for prophylaxis (strength of recommendation)[a]	
	All patients	**Patients with chronic GVHD**
Bacteria	Broad-spectrum antibiotic(s) during period of neutropenia (ANC < 500/μL). Choices include a single agent, such as levofloxacin or ceftazidime, or a combination of agents, such as piperacillin. [CIII] Patients with hypogammaglobulinemia: Intravenous immunoglobulin administered at 1- to 4-week intervals depending on level. [CIII]	Penicillin VK twice daily for encapsulated organisms. [BIIb] Alternatives: TMP/SMX daily, azithromycin three times per week. [CIII] Patients with hypogammaglobulinemia or repeated sinopulmonary infections: Intravenous immunoglobulin administered at monthly intervals depending on level. [CIII]
Fungi	Fluconazole from start of conditioning to day 75 (allogeneic HCT) or day 30 (autologous HCT). [AIa]	Mold active agents, such as posaconazole when prednisone dose is ≥ 1 mg/kg. [AI]
PCJ	TMP/SMX is the drug of choice and starts 1–2 wk before transplant until 48 h before HCT, then from engraftment until 6 months after HCT if no chronic GVHD. Alternatives: dapsone, atovaquone, pentamidine. [AIb]	TMP/SMX in a variety schedules. [AIb]
HSV (seropositive patients)	Acyclovir prophylaxis from start of conditioning until day 30. Alternatives: valacyclovir. [AI]	Not indicated
VZV (seropositive)	Acyclovir prophylaxis from start of conditioning until 1 year after HCT for those with a history of natural infection. Alternative: valacyclovir. [AIa]	Acyclovir from start of immune suppression until completion. Alternatives: valacyclovir. [AIa]
CMV (seropositive)	Ganciclovir prophylaxis or preemptive therapy based on plasma CMV DNA detection by PCR between engraftment and day 100. Foscarnet is an equally effective alternative to ganciclovir for preemptive therapy. [AI]	Valganciclovir therapy based on plasma CMV DNA detection by PCR until dose of prednisone is < 1 mg/kg. [BIII]
CMV (seronegative)	Preferential use of preemptive therapy with ganciclovir or foscarnet as outlined for seropositive patients. [BII]	Not indicated

[a]Evidence-based grading system adapted from Couriel D, Carpenter PA, Cutler C, et al: Ancillary therapy and supportive care of chronic GVHD: NIH Consensus Development Project on criteria for clinical trials in chronic GVHD: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant* 12:375–396, 2006.
Recommendations are "A," should always be offered; "B," should generally be offered; "C," optional; "D," should generally not be offered. Evidence is "level I" if it is derived from ≥ 1 properly designed randomized, controlled trial; "level II" if it is derived from ≥ 1 well-designed clinical trial without randomization, from cohort or case-controlled analytical studies, or from multiple time series or dramatic results from uncontrolled experiments; and "level III" if it is derived from opinions of respected authorities based on clinical experience. Qualifiers, "a," indicates that evidence is directly from study(s) in GVHD, or "b" if the evidence was derived indirectly from study(s) in analogous or other pertinent disease.
ANC, absolute neutrophil count; CMV, cytomegalovirus; DS, double strength; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HSV, herpes simplex virus; IgG, immunoglobulin G; IV, intravenous; max, maximum dose; MTX, methotrexate; PCJ, *Pneumocystis jiroveci* pneumonia; PCR, polymerase chain reaction; SMX, sulfamethoxazole; TMP, trimethoprim; VK, V potassium; VZV, varicella zoster virus.

heightens the risk of blood infections with organisms that colonize the skin, such as coagulase negative *staphylococci* or *Candida spp.*, and gastrointestinal mucosal damage increases the risk of infections with enteric organisms, such as *Escherichia coli*. *Clostridium difficile* toxic colitis can be a common infection in transplant patients, particularly those patients in intensive care units. Patients with a history of prolonged neutropenia prior to HCT are at risk for developing fungal infections involving the skin, lung, sinuses, which typically are a mold such as *Aspergillus*, or the liver and spleen, typically *Candida* spp. The most likely viral infection in this period is herpes simplex virus. Fever of unknown origin also occurs commonly during the neutropenic period. Prophylactic systemic antibiotics conventionally are administered to reduce the risk of bacteremia during the neutropenic period, although improvement in survival has not been demonstrated [77,78]. Administration of growth factors, such as granulocyte colony-stimulating factor, shortens the duration of neutropenia, but there is little evidence for improvement in outcome [79].

Following Engraftment Period

The period following engraftment (30 to 100 days posttransplant) is characterized by skin and mucosal damage and compromised cellular immunity related to GVHD and its treatment. Viral (CMV) and fungal (*Aspergillus, Pneumocystis jiroveci*) infections predominate during this period. Gram-negative bacteremias related to GVHD-associated mucosal damage and Gram-positive infections due to indwelling catheters remain a risk. Other causes of fever of unknown origin after engraftment include occult sinusitis, hepatosplenic candidiasis, and pulmonary or disseminated *Aspergillus* infection.

Late Phase

The late phase (greater than 100 days posttransplant) is characterized by a persistently impaired cellular immunity in patients with chronic GVHD. Patients with chronic GVHD are highly susceptible to recurrent bacterial infections, especially from encapsulated bacteria, including *Streptococcus pneumonia, Haemophilus influenzae*, and *Neisseria meningitides* (functional asplenia). Bronchopulmonary infections, septicemia, and ear, nose, and throat infections occur. Common nonbacterial infections at this time include varicella zoster, CMV, *P. jiroveci*, and *Aspergillus*.

Evaluation and Treatment

Signs and symptoms of infection may be diminished in patients who are neutropenic or receiving immunosuppressive drugs [80]. Thus, preemptive antibiotic therapy should be instituted promptly for any fever during the neutropenic period, because infections can progress rapidly to a fatal outcome [81]. The febrile patient should be examined thoroughly for source of infection, including the oral cavity, perianal tissue, and skin surrounding the central venous catheter. Cultures should be obtained of blood, urine, and stool if diarrhea is present, and chest radiograph should be performed. Antibiotic therapy should provide empiric coverage for the most common organisms, Gram-positive bacteria that colonize the skin and oral cavity, as well as the less common but more virulent Gram-negative bacteria that arise from the GI tract [78,80,81]. Broad-spectrum antibiotic therapy should be continued through the duration of neutropenia, even if fever resolves. If fever persists, the antibiotic regimen should be broadened after 4 days to provide empiric treatment of fungi. *C. difficile* infection should be considered in patients with diarrhea and can be treated with oral metronidazole.

Evaluation of persistent fevers after granulocyte recovery should consider occult sources of bacterial infection, such as sinuses, perirectal tissue, or central venous lines, as well as viral or fungal etiologies. Removal of the central venous catheter is occasionally required. Viral infections must be considered in patients with GI symptoms and may involve the esophagus, upper and lower intestines, or liver [82]. The diagnosis is established by biopsy or brushings taken from the center of the lesions so as to include infected endothelial cells and submucosal tissue. Host immunosuppression associated with GVHD and its treatment predisposes patients to a variety of opportunistic infections. Patients with active chronic GVHD should receive prophylaxis for *P. jiroveci* pneumonia with trimethoprim–sulfamethoxazole and for encapsulated organisms with daily trimethoprim–sulfamethoxazole, penicillin, or azithromycin. Infectious causes of pulmonary infiltrates must be differentiated from noninfectious causes to ensure prompt institution of appropriate therapy [48,83].

BAL should be performed without delay to establish the etiology of diffuse infiltrates, unless clearly related to pulmonary edema [84]. BAL specimens should be assayed for the presence of common nosocomial bacteria as well as *Legionella*, *Mycobacteria*, and *Nocardia; P. jiroveci*; fungi other than *P. jiroveci* pneumonia; respiratory viruses; and herpes group viruses by cultures and immunocytochemical stains. Focal pulmonary infiltrates that occur after HCT are most frequently caused by infection, particularly fungal infection [85]. Evaluation of a focal infiltrate should include a CT scan to delineate the number and extent of infiltrates. BAL should be performed as a first step because the procedure is minimally invasive and historically has produced a diagnosis in 50% of patients with fungal lesions using standard diagnostic approaches, although the predictive value of negative results was poor [84]. At some centers, the increasing use of more diagnostic approaches like galactomannan antigen testing [86] or, ongoing development of molecular methods to detect fungi or viral pathogens (e.g., human metapneumovirus [87,88]) continues to improve the yield of BAL. As a result, the number of lung biopsies performed at these centers has declined. Transbronchial biopsy is not recommended because it has not been shown to improve sensitivity in these situations, and often thrombocytopenia precludes the ability to perform the procedure safely. Percutaneous fine-needle aspiration is indicated for diagnosis of peripheral infiltrates that cannot be evaluated by BAL. Fine-needle aspiration has a sensitivity of approximately 67% for diagnosis of fungal infection, but it has a poor negative predictive value. If the diagnosis is not ascertained after BAL or fine-needle aspiration, a biopsy is required [89]. Specimens should be evaluated histologically and undergo testing for bacteria, fungi, and viruses by appropriate cultures and immunocytochemical stains as noted previously. Surgical resection of a solitary fungal lesion may improve the chances for cure [90].

Opportunistic Infections

Pneumocystis jiroveci **Pneumonia.** Inadequate cell-mediated immunity poses a risk for development of *P. jiroveci* pneumonia infection after HCT [91]. Recommendations for prevention of PJP are found in Table 188.2 [77,92].

Fungal Infections

Factors that predispose to invasive yeast infections include neutropenia, mucosal barrier disruption, and broad-spectrum antibiotics that promote colonization of the GI mucosa [93]. Candidal infections generally occur within the first 3 weeks after HCT, coinciding with the period of neutropenia, although a second period of risk occurs during treatment for chronic GVHD. Invasive candidiasis may involve the liver and spleen, with potential for dissemination to kidneys or rarely, the CNS

[94,95]. The diagnosis of invasive candidiasis is difficult because blood cultures are negative in approximately one half of the cases with organ involvement. Recommendations for prevention of candidiasis are found in Table 188.2. Fluconazole is effective for treatment of the most common *Candida* spp, *C. albicans* and *C. tropicalis* [96,97] (see Table 188.2), but does not prevent or treat infection with *C. glabrata*, *C. krusei*, or *C. parapsilosis*. Removal of the central venous catheter should be considered when *Candida sp*. is isolated from blood cultures. Fungal vegetations on heart valves are possible and echocardiography is often considered. Lipid-complexed amphotericin products, echinocandins, or other azoles may be useful alternatives [98].

Invasive mold infections develop in up to 20% of patients after HCT [99]. The incidence of *Aspergillus* infections is highest within the first month after HCT, and there is a second peak incidence during chronic GVHD. *Aspergillus* infections have been difficult to diagnose by standard methods, and more than 20% of the cases have been diagnosed only at autopsy. Cultures of BAL fluid are negative in 50% of pulmonary disease; therefore, the diagnosis frequently requires a biopsy of affected tissues [85]. The *Aspergillus* Galactomannan Enzyme Immunoassay detects a polysaccharide secreted from *Aspergillus hyphae* and is a useful screening tool, with a sensitivity of 65% and specificity of 95% [100]. High-risk patients, those with severe GVHD treated with high-dose corticosteroids, should be given prophylaxis with agents like voriconazole or posaconazole which is active against aspergillosis and certain other molds. Because invasive aspergillosis is associated with a high mortality rate, documented or suspected infections should be treated aggressively with voriconazole, lipid-complexed amphotericin products, or combination therapy [101,102]. Surgical removal of infected tissue should be restricted to cases of circumscribed disease [103].

Viral Infections

Cytomegalovirus. Protection from exposure by use of seronegative or leukocyte-reduced blood components has reduced the incidence of CMV infection among seronegative patients [21], whereas ganciclovir has been shown to be an effective agent for prevention of CMV disease in seropositive patients [104–106] (see Table 188.2). Ganciclovir should be initiated as prophylaxis after engraftment, with careful monitoring of the patient for marrow suppression, a side effect that can lead to life-threatening infection (Table 188.2) [107]. A reasonable alternative is to monitor for CMV reactivation with serum PCR assays, followed by prompt institution of ganciclovir when the CMV copy number reaches a positive threshold [108–110]. Generally, surveillance CMV PCR testing is performed weekly from transplant day 0 through day 100; however, monitoring generally is continued for CMV positive patients on high-dose corticosteroids.

Although prophylaxis greatly reduces the risk for CMV disease, severe pneumonitis, gastroenteritis, hepatitis, or bone marrow failure continue to occur in a small proportion of patients [111]. The diagnosis of CMV pneumonitis can be established in most patients by PCR assay or rapid shell vial culture of BAL fluid [112]. CMV enteritis is often indistinguishable from GVHD clinically, and the diagnosis relies on endoscopic evaluation [113]. CMV enteritis appears as ulcerations of the esophagus, stomach, or intestines. Viral cultures and histologic stains of the affected tissue are used to establish the diagnosis. Treatment of CMV infection includes ganciclovir (foscarnet or cidofovir are acceptable alternatives) in combination with immune globulin [114,115]. Foscarnet can be used in place of ganciclovir if significant marrow toxicity occurs or drug resistance is identified.

Herpes Simplex Virus. Herpes simplex virus (HSV) is the most common cause of infectious mucositis after HCT and may cause life-threatening encephalitis, hepatitis, or pneumonia in immunocompromised patients [116–118]. HSV pneumonitis or hepatitis is associated with high mortality rates; although less serious, HSV mucositis produces severe local pain and swelling. Acyclovir prophylaxis has been shown to be very effective for prevention of HSV reactivation in seropositive patients and for treatment of established disease [119,120] (see Table 188.2).

Varicella Zoster Virus. Varicella zoster virus (VZV) causes life-threatening disease in immunocompromised patients, as a primary infection or reactivation of endogenous virus [121]. Exposed seronegative patients should receive VZV immune globulin within 96 hours if available, and acyclovir should be administered from days 3 to 22 after exposure [122]. Among seropositive patients, VZV reactivation occurs in approximately 40%, with the highest incidence around 5 months after HCT [121,123]. Prophylaxis with acyclovir is recommended for seropositive patients until 1 year after HCT or until complete discontinuation of immunosuppressive therapy for chronic GVHD immunity [124] (see Table 188.2). VZV infection typically causes local skin involvement, but it can disseminate in immunocompromised patients, resulting in pneumonitis, esophagitis, pancreatitis, hepatitis, or encephalitis [125–128]. VZV hepatitis may present as a syndrome of fever, severe abdominal pain, and elevated aminotransferase levels, and because it is associated with a high mortality rate, should be treated presumptively with high-dose acyclovir [128]. For localized infection, a short course of intravenous acyclovir for 24 to 48 hours can be followed by oral valacyclovir for the duration of therapy.

Respiratory Viruses. Respiratory viruses may spread quickly within HCT patient populations, causing epidemics of life-threatening infection. Respiratory syncytial virus (RSV), influenza, and parainfluenza are the most frequently encountered respiratory viruses in these situations [129]. Symptoms of upper respiratory infection should prompt cultures of nasopharyngeal secretions, careful monitoring for progression of disease, and isolation to prevent spread to other patients. Patients in the period before engraftment are at greatest risk for progression to lower tract disease with RSV. Once lower-tract disease occurs, however, mortality is high regardless of engraftment status [130]. If lower-tract disease is suspected, BAL should be performed to obtain samples for viral fluorescence antibody and PCR tests and viral cultures [131].

Adenovirus. Adenovirus and polyoma BK virus are common causes of hemorrhagic cystitis after HCT [66]. When disseminated, adenovirus can cause hemorrhagic enterocolitis, interstitial pneumonitis, myocarditis, nephritis, meningoencephalitis, or severe hepatitis [132]. Adenoviral infections occur more commonly in children and after allogeneic grafts [133]. Patients with poor T-cell function, such as recipients of T cell–depleted grafts or those receiving intensive immune suppressing therapies, are at greatest risk for disseminated infection. Disseminated infections are often difficult to detect by viral cultures, and PCR assays may be more useful [134]. The most promising treatment results have been reported after administration of cidofovir, although renal insufficiency is a potential side effect [135]. Polyoma BK virus should be considered in the differential diagnosis of renal insufficiency in patients on chronic immune suppression, and can be diagnosed by renal biopsy.

Epstein-Barr Virus. Epstein–Barr virus (EBV) seropositive immunocompromised patients are at risk for development of life-threatening lymphoproliferative disease (LPD) after HCT

[136]. The risk for EBV–LPD is highest among patients who receive T-cell–depleted grafts or who are given intensive immune suppression for treatment of GVHD [137]. The diagnosis is made by biopsy of enlarged nodes or affected tissue. A presumptive diagnosis can be made in high-risk patients who have clinical symptoms and elevated plasma or cellular EBV DNA copy number [138]. The mainstay of therapy is reduction or elimination of immunosuppressive therapy to allow reconstitution of EBV-specific T-cell immunity. However, it may not be feasible to eliminate immunosuppression therapy without risking a flare of life-threatening GVHD. Some studies have shown encouraging results with mAb directed against CD20, which targets EBV-infected B cells [139]. EBV–LPD that develops in recipients of T cell–depleted grafts may be ameliorated by infusion of donor T lymphocytes [140].

Graft Rejection

Graft rejection presents as failure to recover hematopoiesis after transplantation, termed *primary graft failure*, or as the loss of an established donor graft, termed *secondary graft failure*. Persistence of neutropenia (an absolute neutrophil count of more than 100 cells per μL) after day 26 is associated with increased risk of early mortality [141]. Although the molecular and cellular mechanisms are not completely understood, graft rejection appears to be mediated preferentially by recipient T cells [142]. Another described mechanism includes rejection mediated by host natural killer cells which, to some extent, can be overcome by the preparative regimen. Finally, alloimmune antibodies in sensitized recipients may cause rejection in mice but their role in humans is controversial. Donor HLA disparity stimulates strong alloreactive immune responses in the immunocompetent recipient and increases the risk for graft rejection. Donor T cells counteract the rejection responses of host alloreactive cells that have survived the conditioning regimen [143]. Higher stem cell doses facilitate engraftment, particularly when T cell–depleted grafts are used [144,145].

Quantitation of donor engraftment (donor chimerism), using PCR-based techniques to detect donor-specific variable nucleotide tandem repeats (VNTR) sequences, may be helpful in determining whether the graft has been rejected, in which case the peripheral blood T cells will be primarily of host origin, or whether the donor graft is not functioning, in which case the cells will be of donor origin. In the latter case, other causes of graft suppression should be considered, including relapse, medications such as ganciclovir or trimethoprim–sulfamethoxazole, mycophenolate mofetil, or viral infections such as CMV, human herpes virus 6, or parvovirus B19. In either case, graft failure after myeloablative conditioning is a life-threatening complication because autologous reconstitution is uncommon and results in death from hemorrhage or infection. A range of cellular therapies have been used to overcome rejection ranging from donor lymphocyte infusions in the case of declining donor T-cell chimerism, possibly combined with immunosuppressive therapy. In fulminant rejection, retransplantation is necessary, using the same or another donor. Conditioning should preferentially differ from that used at the first transplant to avoid unnecessary toxicity, and a high graft cell dose should be targeted [142].

Graft-Versus-Host Disease

The most significant immunologic barrier to successful HCT is the graft-versus-host reaction, which can result in life-threatening inflammation and tissue destruction. Donor T cells that recognize disparate recipient alloantigens are the central mediators of GVHD. The most important alloantigens are those encoded by the major histocompatibility complex, or HLA system, although non-HLA antigens may certainly be involved. Despite the significance of GVHD as a complication of HCT, patients who develop GVHD have lower relapse rates than patients without GVHD, and this can also be explained by an immunologically mediated graft-versus-tumor (GVT) effect that helps eradicate the underlying malignancy.

Acute Graft-Versus-Host Disease

The incidence and severity of acute GVHD are determined primarily by the degree of HLA disparity and influenced by the nature of GVHD prophylaxis [146–148]. Severe acute GVHD (grades III to IV) develops in 15% of recipients transplanted from HLA-identical sibling donors, and in a greater proportion of those given unrelated or mismatched grafts. Acute GVHD typically begins abruptly at 2 to 4 weeks after myeloablative HCT and generally occurs before day 100, but the onset may be delayed after nonmyeloablative HCT. The clinicopathologic syndrome is consistent with various combinations of inflammatory dermatitis, enteritis, and hepatitis, which reflect the pathophysiology of T-cell activation with generation of cytotoxic lymphocytes and elaboration of inflammatory cytokines that cause tissue damage. The severity of acute GVHD in the three main target organs (skin, liver, and GI tract) is staged 1 through 4 based on accepted criteria that primarily include the extent of rash, magnitude of hyperbilirubinemia, and volume of diarrhea. The various combinations of skin, liver, and GI involvement can then be used to assign an overall grade of GVHD: grade I being mild, and grade IV being life threatening [149,150] (Table 188.3). When cellular injury is severe, GVHD of the skin may manifest with bulla formation and skin ulceration. In the GI tract, symptoms range from mild anorexia, to nausea and vomiting, or to severe bloody diarrhea with cramping periumbilical pain.

Chronic Graft-Versus-Host Disease

Chronic GVHD (CGVHD) occurs in approximately 30% to 60% of transplant recipients, more often when the donor is not an HLA-identical sibling and when there is a history of acute GVHD [151]. There is a higher risk for developing CGVHD with growth factor–mobilized PBSC grafts compared to marrow grafts [152]. CGVHD also is more likely when the recipient or donor is older or CMV seropositive, or in a male patient who receives HSC from a multiparous female donor. Risk factors for mortality at the time of diagnosis of CGVHD include: platelet counts less than 100×10^9 per L, greater than 0.5 mg per kg per day prednisone, serum total bilirubin greater than 34 μmol per L, older recipient, prior acute GVHD, older donor, and graft-versus-host HLA mismatching [153,154].

CGVHD is defined without reference to time after HCT, but by the presence of hallmark CGVHD features, which resemble autoimmune diseases such as systemic sclerosis, Sjogren's syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency [155] (Table 188.4). Simply stated, the distinction of chronic from acute GVHD requires the presence of at least one diagnostic clinical sign of CGVHD or presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests. The overall severity of CGVHD is determined by a 0- to 3-point score (none, mild, moderate, severe) that reflects the clinical effect of CGVHD on the patient's functional status in any number of different organs. CGVHD frequently involves the skin, liver, eyes, mouth, upper respiratory tract, lungs, and esophagus. Less frequently, serosal surfaces, lower GI tract, female genitalia, or fascia are involved. Major causes of morbidity include scleroderma, contractures, ulceration, keratoconjunctivitis, strictures, obstructive pulmonary disease, and weight loss. Uncontrolled chronic GVHD

TABLE 188.3

CLASSIFICATION OF GRAFT-VERSUS-HOST DISEASE

Acute GVHD organ staging			
Organ	**Stage**	**Scores**	**Description**
Skin	1		≤25% body surface area with maculopapular rash
	2		25%–50% body surface area with maculopapular rash
	3		≥50% body surface area with maculopapular rash or erythroderma
	4		Generalized erythroderma with bullae
Liver	1		Bilirubin 2.0–3.0 mg/dL
	2		Bilirubin 3.0–5.9 mg/dL
	3		Bilirubin 6.0–14.9 mg/dL
	4		Bilirubin rise to ≥15 mg/dL
GI tract			Stage is assigned according to a total GI score based on volume of diarrhea, presence of bloody stool, and abdominal pain or cramping
	1		Total GI score of 1
	2		Total GI score of 2
	3		Total GI score of 3–4
	4		Total GI score of 5–7
GI scoring			Diarrhea volume averaged over 3 d Adult (mL/d), child[a] (mL/kg/d)
		+1	>500–999, >10–20
		+2	1,000–1,499, >20–30
		+3	>1,500, >30
		+2	Score additional 2 points for presence of abdominal pain or cramping
		+2	Score additional 2 points for presence of bloody stools

Acute GVHD overall grade	Skin stage	Liver stage	GI stage
I	1–2	0	0
II	3 or	1 or	1
III		2–3	2–3
IV	4 or	4 or	4

[a]Children < 17 years of age who are < 1.73 m^2.
GI, gastrointestinal; GVHD, graft-versus-host disease.
Adapted from Martin PJ, Nelson BJ, Applebaum FR, et al: Evaluation of a CD5-specific immunotoxin for treatment of acute graft-versus-host disease after allogeneic marrow transplantation. *Blood* 88(3):962–969, 1996, with permission.

interferes with immune reconstitution and is strongly associated with increased risks of opportunistic infections and death.

Confirming the Diagnosis of Graft-Versus-Host Disease

Unlike CGVHD, the clinical signs of acute GVHD are not considered sufficiently pathognomonic to establish the diagnosis, especially when there is isolated organ involvement. However, the combination of rash, nausea, and voluminous diarrhea, occurring at the time of, or early after, neutrophil engraftment makes the diagnosis very likely. The differential diagnosis involves ruling out other causes of rash, diarrhea or liver toxicity as listed in Table 188.5. Tissue biopsies of the skin, liver, or stomach are recommended to confirm a histologic diagnosis of GVHD and, most importantly, to exclude opportunistic infection; however, the interpretation of biopsies performed within 3 weeks of myeloablative therapy may be problematic because it is difficult to separate cellular injury induced by chemoradiotherapy from GVHD. The gastric antral mucosa provides the most sensitive site for evaluation of intestinal GVHD and is preferred over duodenal and rectal biopsy because there is less risk for bleeding complications. The histologic hallmark of GVHD-induced cellular injury is apoptosis, observed in epidermal basal keratinocytes, bile duct or intestinal crypt epithelial cells, and often associated with infiltration by lymphocytes [156–158]. Biopsy is unnecessary to confirm the presence of chronic GVHD if at least one diagnostic feature is present, but histologic confirmation or other pertinent testing is necessary when CGVHD features are only distinctive or suggestive (see Table 188.4).

Prevention of Graft-Versus-Host Disease

GVHD prevention strategies are almost always incorporated into the overall treatment plan, and these include optimizing the choice of allogeneic donor and stem cell product based on known risk factors for GVHD, T-cell depletion of the donor HSC graft as discussed earlier, or, most commonly, post-transplant immunosuppression. Adjunctive therapy with ursodeoxycholic acid may improve liver function and a randomized placebo-controlled multicenter study demonstrated that prophylaxis with ursodeoxycholic acid reduced hepatic problems, severe acute GVHD, and improved survival after allogeneic HCT [159].

TABLE 188.4

CLASSIFICATION OF SYMPTOMS AND SIGNS OF CHRONIC GRAFT-VERSUS-HOST DISEASE

Organ or site	Diagnostic	Distinctive[a]	Common[b]
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen-sclerosis–like features	Depigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss[c]	
Scalp and body hair		New onset of scalp alopecia Scaling, papulosquamous lesions	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening	Xerostomia Mucocele Mucosal atrophy Pseudomembranes[c] Ulcers[c]	Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful[d] Cicatricial conjunctivitis Keratoconjunctivitis sicca[d] Confluent punctate keratopathy	
Genitalia	Lichen-planus–like features Vaginal scarring or stenosis	Erosions[c] Fissures[c] Ulcers[c]	
GI tract	Esophageal web Esophageal strictures or stenosis in upper to mid third[c]		Anorexia, nausea vomiting, diarrhea, Failure to thrive
Liver			Bilirubin > 2 × ULN Alk Phosp > 2 × ULN AST/ALT > 2 × ULN
Lung	Bronchiolitis obliterans based on lung biopsy	Bronchiolitis obliterans based on PFTs + radiology[d]	BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis	
Features acknowledged as part of chronic GVHD symptomatology if the diagnosis is already confirmed			
Skin	Sweat impairment, ichthyosis, keratosis pilaris, hypopigmentation, hyperpigmentation		
Hair	Thinning scalp hair, typically patchy, coarse, dull not explained by endocrine or other causes, premature gray hair		
Eyes	Photophobia, periorbital hyperpigmentation, blepharitis		
GI tract	Exocrine pancreatic insufficiency		
Muscles/Joints	Edema, muscle cramps, arthralgia, or arthritis.		
Hematology	Thrombocytopenia, eosinophilia, lymphopenia		
Immune	Lymphopenia, hypo- or hypergammaglobulinemia, autoantibodies (AIHA, ITP)		
Other	Pericardial/pleural effusions, ascites, peripheral neuropathy, nephrotic syndrome, myasthenia gravis, cardiac conduction abnormality, or cardiomyopathy		

[a] Seen in chronic GVHD but are insufficient alone to establish the diagnosis.
[b] Seen in both acute and chronic GVHD alone to establish a diagnosis of chronic GVHD.
[c] In all cases must exclude infection, drug effects, malignancy, or other causes.
[d] Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer's test for eyes).
AIHA, autoimmune hemolytic anemia; ALT, alanine aminotransferase; AST aspartate aminotransferase; BOOP, bronchiolitis obliterans with organizing pneumonia; GI, gastrointestinal; ITP, idiopathic (immune) thrombocytopenic purpura; PFTs, pulmonary function tests; ULN, upper limit of normal range for age.
Modified from Filipovich AH, Weisdorf D, Pavletic S, et al: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 11(12):945–956, 2005, with permission.

TABLE 188.5

DIFFERENTIAL DIAGNOSIS OF ACUTE GRAFT-VERSUS-HOST DISEASE (AGVHD)

AGVHD manifestation	Differential diagnosis
Rash	Drug reaction Allergic reaction Infection Regimen-related toxicity
Diarrhea	Infection (viral, fungal) Narcotic bowel syndrome (opiate withdrawal)
Abdominal pain	Acute pancreatitis Acute cholecystitis (biliary sludge, stones, infection) Narcotic bowel syndrome (opiate withdrawal)
Elevated liver enzymes	Sinusoidal obstruction syndrome Medication toxicities (e.g., cyclosporine) Cholangitis lenta (sepsis) Biliary sludge syndrome Viral infections (CMV, EBV, hepatitis B) Hemolysis

CMV, cytomegalovirus; EBV, Epstein–Barr virus.

Postgrafting Immunosuppression. In the absence of T-cell depletion, posttransplant immune suppression must be administered to control donor alloreactive T cells. Standard prophylaxis regimens deliver a 6-month course of cyclosporine or tacrolimus combined with a short course of methotrexate administered intravenously on the 1st, 3rd, 6th, and 11th days after HCT [147]. After myeloablative conditioning, methotrexate toxicity may exacerbate RRT in high turnover cells such as in oral and intestinal mucosae and hepatocytes. Some patients, particularly those with the C677T polymorphism in the methylene–tetrahydrofolate reductase gene, have more severe mucositis and slower platelet engraftment when given methotrexate [160]. Variations of CNI plus methotrexate include CNI plus mycophenolate mofetil [147,161]. or, tacrolimus and sirolimus, with or without methotrexate [162–164]. Steady-state serum CNI and sirolimus levels require monitoring. Dose reductions should be made when toxicities emerge or when serum trough levels exceed the upper limit of the therapeutic range.

Treatment of Graft-Versus-Host Disease

Despite GVHD prophylaxis regimens, 30% to 80% of allogeneic HCT recipients develop acute GVHD and require additional therapy with glucocorticoids.

Acute Graft-Versus-Host Disease. Glucocorticoids have been the mainstay of primary therapy for acute GVHD. Initial starting doses have been recently calibrated to the severity and extent of organ involvement as demonstrated by one large retrospective study [165]. This approach requires further validation, particularly for grades III and IV acute GVHD. For the one third of patients who develop GVHD without liver involvement, and whose GI symptoms are defined as stage 1 (anorexia, nausea, or vomiting with peak stool volume less than 1,000 mL per day), with or without rash involving less then 50% of the body surface, treatment may reasonably begin at 1 mg per kg per day methylprednisolone (or oral equivalent) combined with topical and minimally absorbed glucocorticoids (beclomethasone or budesonide). When there is liver involvement, or when intestinal and skin GVHD is greater than defined above, methylprednisolone is typically begun at a dose of 2 mg per kg per day for 14 days, by which time rash, diarrhea, abdominal pain, and liver dysfunction usually remit and a glucocorticoid taper is considered appropriate. In patients with GI hemorrhage, surgery very rarely is indicated, and the mainstay of therapy is initiation of immune suppression, along with the infusion of appropriate blood components [166,167]. Several studies, including a randomized trial, have shown no benefit for administration of doses greater than 2 mg per kg per day of methylprednisolone [168,169]. The results of a recent multicenter randomized phase II trial suggested that response and early survival after standard therapy with prednisone might be improved by adding mycophenolate mofetil [170]. A follow-up phase III study to more definitively evaluate this finding is imminent.

Chronic Graft-Versus-Host Disease. In practice, systemic therapy is considered when chronic GVHD is present in more than two organs, or there are moderate to severe abnormalities of a single organ with functional impairment (Table 188.6). In contrast, systemic therapy is generally not warranted for patients with mild abnormalities of one or two organs that do not cause functional impairment. For example, jaundice, or marked elevations of liver enzymes or skin manifestations that are not extensive. However, mild chronic GVHD does warrant systemic therapy when either thrombocytopenia or steroid treatment is present at diagnosis.

Standard primary therapy for clinical extensive CGVHD usually begins with glucocorticoids and extended administration of a CNI. After newly diagnosed CGVHD manifestations have been controlled by daily glucocorticoids, the judicious use of glucocorticoids at the lowest effective dose and alternate-day administration can minimize steroid-related side effects. The median duration of systemic immunosuppression for the treatment of CGVHD approximates 2 to 3 years [153]. Longer therapy tends to be required for recipients of peripheral blood stem cells, male patients with female donors, multiple organ

TABLE 188.6

INDICATION FOR SYSTEMIC IMMUNOSUPPRESSION AT DAY 80

Global severity of chronic GVHD	High-risk features[a]	Systemic therapy
None	Yes	None[b]
Mild (< 3 sites[c], no lung)	No	No
Mild	Yes	Yes
Moderate[d] (or mild lung) or severe[e]	Yes or no	Yes

[a] Less than 100,000 platelets/μL, progressive onset (on prednisone).
[b] Need to balance risks and benefits of graft-versus-tumor against risks of developing more severe chronic GVHD based on the coexistence of risk factors, including unrelated or mismatched-related donor, female donor, and peripheral blood stem cell transplant.
[c] No clinically significant functional impairment (score ≤ 1 in each site).
[d] At least one site functionally impaired without major disability (Score 2) or 3 or more sites without clinically significant functional impairment (each with score ≤ 1).
[e] Major disability at any site (score 3, or score ≥ 2 in lung).
GVHD, graft-versus-host disease.

TABLE 188.7

THERAPY OPTIONS FOR STEROID-REFRACTORY ACUTE GRAFT-VERSUS-HOST DISEASE

Therapy	Comments
Systemic	
Polyclonal	
Antithymocyte globulin (ATGAM,[a] Thymoglobulin[b])	Delayed use appears to be very ineffective. Skin responds best.
Monoclonal	
Anti-CD3 (OKT3,[c] visilizumab[d,e])	Currently used infrequently.
Anti-IL2 (daclizumab,[d] basiliximab[f])	Depletes conventional and regulatory T cells.
Anti-TNFα (infliximab[f])	Consider early for refractory lower GI tract.
Anti-CD52 (alemtuzumab[d])	Depletes T & B cells (lower risk EBV PTLD)
Anti-CD2 (alefacept[g])	Depletes memory T cells; needs further study.
Fusion proteins	
Anti-IL2 (denileukin diftitox)	Anti-T cell but also depletes regulatory T cells.
Anti-TNFα (etanercept)	
Macrolides and antimetabolites	
Tacrolimus	Inhibits conventional and regulatory T cells
Sirolimus	Inhibits conventional but not regulatory T cells.
Mycophenolate mofetil	Enteric coated formulation may minimize toxicity but liquid formulation not available
Extracorporeal photopheresis	Mechanism includes facilitation of regulatory T cells Particularly effective in skin, infrequently associated with opportunistic infections.
Mesenchymal stem cells	Mechanism poorly understood but thought to modulate tissue repair.
Topical	
Glucocorticoids	
Budesonide	Useful as steroid-sparing agent in lower GI tract.
Beclomethasone[e]	Useful as steroid-sparing agent in upper GI tract
PUVA	Useful for skin only involvement.

[a]Equine.
[b]Rabbit.
[c]Murine.
[d]Humanized.
[e]Not commercially available.
[f]Chimeric murine–human.
[g]Human IgG1-fusion protein.

involvement at the onset of CGVHD, graft-versus-host HLA mismatching, and hyperbilirubinemia.

Within 3 years of primary therapy, just over one quarter of the patients have resolved CGVHD, 1 out of 10 patients will continue primary therapy beyond 3 years and one-third require secondary treatment with a variety of other immunosuppressive agents [171]. The remaining patients develop recurrent malignancy or die from nonrelapse causes. Infection from a broad array of pathogens is the major cause of nonrelapse mortality, followed by progressive organ failure from CGVHD involvement. Therefore, antibiotic prophylaxis to prevent infection (Table 188.2) and supportive care to minimize morbidity and prevent disability are critically important components of CGVHD management [172].

Steroid-Refractory Graft-Versus-Host Disease. Glucocorticoids often fail to control acute GVHD manifestations such that 40% to 60% of patients have steroid-refractory (SR) acute GVHD. SR-GVHD has been defined operationally as the progression of acute GVHD symptoms beyond 3 days after starting methylprednisolone. Persistence of GVHD beyond 7 to 14 days also should be considered failure of response. The prognosis of acute GVHD can be related to its overall severity (grade) and response to glucocorticoids [173,174]. It is of no surprise that grade III and IV SR acute GVHD, especially with visceral involvement, requires urgent initiation of effective secondary therapy.

Unfortunately, there is no generally accepted therapy for SR acute GVHD. A full review of the various secondary GVHD therapies is beyond the scope of this review but various approaches are listed in Table 188.7 together with a summary of outcomes (Table 188.8). Polyclonal antithymocyte globulins (ATG), and more recently monoclonal antibodies, are generally used to treat life-threatening visceral manifestations where urgent control of GVHD is necessary. Unfortunately, longer term survival has been unusual when visceral manifestations are severe [175–179]. However, early administration of ATG within 14 days of primary therapy was reported in one study to be associated with improved survival [180]. It has remained difficult to improve the survival after SR-refractory acute GVHD because progressive organ dysfunction is often irreversible, and because second-line therapies constitute a "second hit" to an immune system that has already been impaired by cumulative exposure to high-dose prednisone. In this regard, high daily prednisone doses increase the risk for CMV viremia [181]. Similarly, invasive aspergillosis occurs more frequently in patients

TABLE 188.8

ADVANCES IN THERAPY OPTIONS FOR STEROID-REFRACTORY ACUTE GRAFT-VERSUS-HOST DISEASE (AGVHD)

Treatment	Study design/results	Comments	Reference
Antithymocyte globulin (equine ATG)	Single-arm Phase II studies (N = 29–79) from 1980 to 1999. CR/PR 30% overall (59%–72% for skin), OS 5%–32%.	Responses considerably better in skin than visceral organs. OS worse in visceral or more severe GVHD. One study found OS better if ATGAM given within 14 d of primary therapy (46% vs. 19%, p = 0.05).	[175,180,190,191]
Antithymocyte globulin (rabbit ATG)	Single-arm Phase II (N = 36). 89% had mostly three-system Grade III/IV GVHD. CR/PR 59% overall (96% skin, 46% GI, 36% liver. OS 6%.	Very poor survival. Infections, including 25% EBV PTLD rate, were major problems.	[176]
Daclizumab	Single center Phase I/II (N = 13–57) from 1990s to 2006. CR/PR 51%–92% overall. OS 25%–46%.	Well tolerated. Responses better in children and in skin GVHD. Significant morbidity and mortality due to infections. Patient selection and aggressive antiviral and fungal prophylaxis advised.	[179,192,193]
Denileukin Diftitox	Single center Phase I/II (N = 32). CR/PR 71% overall. OS 30%.	Reversible transaminitis in 22% at MTD. OS 58% (7/12) if achieved CR.	[178]
Infliximab	Single center retrospective (N = 21–32) from 1998 to 2004. CR/PR 59%–82% overall. CR 19%–62%. OS 38%–46% at □1 year.	Well tolerated and active, particularly for GI tract. Better response if age < 35 y and longer interval between HCT and infliximab treatment. High rates of opportunistic infection.	[194–196]
Etanercept	Single center retrospective (N = 13 with AGVHD) from 1995 to 2005. CR (N = 4)/PR (N = 2) 46% overall. OS 67% at median 429 d (range: 71–1,007 d); includes 8 other patients with cGVHD.	Well tolerated. Responses most common in GI tract (64%). CMV reactivation (48%), bacterial (14%) and fungal (19%) infections occurred.	[197]
Psoralen and ultraviolet A (PUVA)	Single center retrospective (N = 103) from 1994 to 2000. CR 24% by intention to treat. OS 51%.	Generally well tolerated but 8 discontinued because of toxicity. CR 37% if tolerated PUVA for 6 wk. PUVA was steroid sparing; 57% did not require additional therapy for skin GVHD.	[198]
Extracorporeal photopheresis (ECP)	Single-center or multicenter phase II or retrospective (N = 21–77) from 1992 to 2006. CR/PR 50%–60%. OS 48%–57%	Best responses in skin (60%–82%) then liver (61%–67%). GI responses variable (0%–75%). Poor Grade IV responses < 15%. AEs during ECP: cytopenias. OS 59%–91% among CRs vs. 11%–12% for non-CRs.	[199–203]
Mycophenolate Mofetil	Single-center retrospective (N = 19–36). CR/PR 42%–72%. OS 16% □–37% □□	Commonest AEs: mild-to-moderate cytopenias. (□at 2 y, □□at 5 y including 12 additional patients with cGVHD)	[204,205]
Sirolimus	Single center pilot trial (N = 21) from 1996 to 1999. High loading dose and/or high maintenance dosing of sirolimus. CR/PR 28% □. OS 34%	□Frequent expected toxicities (cytopenias, hyperlipidemia, HUS) associated with high-serum concentrations likely limited the efficacy. CR/PR 67% among 18 who received ≥ 6 doses.	[206]
Pentostatin	Prospective phase I, single center (N = 23). CR/PR 76%. OS 26% at a median of 85 d (5–1,258 d).	Universal lymphopenia and late infections were dose-limiting. Best responses in skin. Suggested dose for phase II was 1.5 mg/m^2/d × 3 d.	[207]
Mesenchymal stem cells (hMSCs)	European multicenter phase II (N = 55) from 2001 to 2007 of up to 5 doses hMSCs. CR/PR 71%. OS 36% at 2 y. U.S. multicenter phase III hMSC vs. placebo (N = 260). Durable CR 35% vs 30% (p = NS)	No infusion toxicities. OS 53% for CRs in the European study. U.S. study found that hMSCs did not improve durable CR rates (primary endpoint) but hMSCs did improve durable liver CRs (29% vs. 5%, p = 0.046, N = 61) and GI responses (88% vs. 64%, p = 0.018, N = 71)	[208], written communication, Osiris press release

cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; CR, complete response; EBV, Epstein–Barr virus; GI, gastrointestinal; HCT, hematopoietic cell transplantation; HUS, hemolytic uremic syndrome; MTD, maximally tolerated dose; NS, not significant; OS, overall survival; PR, partial response; PTLD, posttransplant lymphoproliferative disorder.

who develop CMV disease and in patients receiving higher doses of prednisone [182]. After nonmyeloablative HCT, high dose prednisone therapy at the time of diagnosis of mold infection has been associated with an increased risk for mold infection-related death [183].

When CGVHD becomes refractory to steroids, in contrast to SR acute GVHD, secondary therapy generally avoids potent antibody therapies unless the manifestations overlap with the disease features typically associated with severe acute GVHD. The time to complete resolution of classical CGVHD manifestations is in the order of weeks to months, and total duration of therapy spans months to years. Therefore, secondary therapies for SR-CGVHD must try to avoid profound T-cell depletion and must generally be more easily delivered chronically in the outpatient setting. Ideally, second-line agents should promote transplantation tolerance so that the morbidity associated with prolonged use of glucocorticoids and other immunosuppressive agents can be minimized.

Promising new agents or strategies that warrant further controlled clinical trials include sirolimus, extracorporeal photophoresis, rituximab, and the platelet-derived growth factor receptor, imatinib, which is of particular interest for the treatment of sclerotic GVHD. A number of ancillary measures that are used with topical intent are often used to target specific organ involvement [172].

Hemolysis

RBC hemolysis may be encountered after HCT and may include more than one etiology. Thrombotic microangiopathy may present as mild hemolysis with RBC fragmentation (schistocytes) or as a more severe form, with thrombocytopenia, renal insufficiency, fever, and altered mental status, similar to hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) [59,184]. Predisposing factors include: endothelial cell injury triggered by chemotherapy, radiation, or immunosuppressive therapy (e.g., CNIs) [59,185]. Drugs such as fludarabine, antithymocyte globulin, or infections with mycoplasma also may produce hemolysis. Unlike the preceding etiologies, hemolysis mediated by major or minor blood group incompatibilities is only seen in recipients of allografts.

Major ABO incompatibility occurs in 30% of allograft recipients and is defined by the presence of isohemagglutinins within recipient plasma that are directed against donor A or B antigens. *Minor* ABO incompatibility also occurs in 30% of recipients and is defined by presence of isohemagglutinins within the donor plasma directed against recipient A or B. *Bidirectional* ABO incompatibility may be present as in the case of a type A recipient and type B donor or vice versa. After successful donor engraftment, the conversion of recipient to donor blood type may take weeks to months because of the relatively long half-life of red blood cells.

Major ABO incompatibility poses a serious risk of severe hemolytic reactions at the time of infusion of the HSC product if preventative steps are not taken. Immediate hemolytic reactions are more likely in the presence of high-level isoagglutinin titers. Therefore, red blood cells are most commonly removed from the graft before infusion to avoid life-threatening hemolysis. Delayed recovery of donor hematopoiesis or hemolysis may occur because recipient plasma cells continue to produce isohemagglutinins for up to several months after HCT [186]. In this case, the diagnosis relies on detection of a positive direct antiglobulin test and the presence of isohemagglutinins directed against donor-type red blood cells. Management of major ABO incompatibility includes the transfusion of group O red blood cells, donor-type platelets, and donor-type plasma until isohemagglutinins against donor-type red blood cells disappear. In the rare cases of ongoing hemolysis due to persistence of donor-directed isohemagglutinins, additional therapy with immunosuppressive agents, erythropoietin, plasma exchange, anti-B-cell antibodies (rituximab), or plasma exchange may be considered [187].

Minor ABO incompatibility poses a risk for mild and self-limited hemolysis at the time of infusion. Delayed hemolysis, seen more commonly after PBSC transplantation, is mediated by clonally expanded donor "passenger lymphocytes" and can present as an abrupt and potentially fatal hemolytic transfusion reaction typically at 1 to 2 weeks after HCT [188,189]. In contrast to major ABO incompatibility, pretransplant donor isohemagglutinin titers do not predict the severity of hemolysis following minor ABO-mismatched HCT. The diagnosis relies again on the detection of a positive direct antiglobulin test and the presence of isohemagglutinins directed against recipient-type red blood cells. To prevent hemolysis, plasma should be removed from the donor HSC product if donor hemagglutinin titers are high. Emergence of donor-derived RBC and isohemagglutinin titers should be monitored after allogeneic HCT. Management of minor ABO incompatibility after HCT includes supportive care with judicious fluid management aimed at preventing acute renal failure, and the transfusion of group O red blood cells and recipient type platelets and plasma. There is no convincing evidence to support the use of plasma exchange.

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CHAPTER 189 ■ CRITICAL CARE OF THE LUNG TRANSPLANT RECIPIENT

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Over the past three decades, lung transplantation (LT) has become a successful therapeutic option for patients with end-stage pulmonary parenchymal or vascular disease. In the early era of LT, the primary complications associated with the procedure were dehiscence and impaired healing of the bronchial anastomosis and early graft failure; these complications occurred in most patients who survived for more than 1 week. Improvements in donor and recipient selection and surgical techniques, the development of new immunosuppressive drugs, and better management of complications, such as primary graft dysfunction (PGD), rejection, and infections have all contributed to advancing the field (Table 189.1). Despite these advances, LT is still associated with numerous complications, often requiring intensive care management.

According to the 2009 report of the International Society for Heart and Lung Transplantation (ISHLT), more than 2,700 lung transplants were performed in 2007 alone. The ISHLT Registry reports that the 1-year survival rate for lung transplant recipients is 79%, the 3-year rate is 64%, and the 5-year rate is 52% [1]. There has been an improvement in median survival in the recent years to 5.7 years over the 4.7 years found in previous years. The most common cause of mortality is PGD in the

TABLE 189.1

MAJOR ADVANCES OR CHANGES IN LUNG TRANSPLANTATION OVER THE PAST FIVE YEARS

Topic	Change	Reference
Transplant procedures by indication	More BLT procedures performed for COPD	[1]
Allocation system	Organs allocated by necessity, not time on waiting list	[7]
Increasing the donor pool	Increasing the use of marginal/extended donors	[15–18]
Primary graft dysfunction	No proven benefit of inhaled nitric oxide administered prophylactically for the prevention of PGD	[31]
	New staging system for PGD	[26]
Immunosuppression	Possible benefit from inhaled cyclosporine	[59]
Rejection	Revision of the staging system for bronchiolitis obliterans syndrome	[62]
Infection prophylaxis	PCR used to monitor for CMV infection following transplant	[74]
	Effective antifungal prophylactic regimens available	[81]
	Twelve months of oral valganciclovir is effective for CMV prophylaxis	[76]
Revision of staging of pathologic rejection	Restaging of lymphocytic bronchiolitis	[58]

BLT, bilateral lung transplantation; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; PCR, polymerase chain reaction; PGD, primary graft dysfunction.

first 30 days following transplantation, non-cytomegalovirus (CMV) infection in the first year following transplantation, and chronic rejection at all subsequent time intervals.

INDICATIONS

Single-lung transplantation (SLT) is performed for obstructive nonsuppurative lung disease, such as emphysema resulting from tobacco use or α_1-antitrypsin deficiency. It is also indicated for fibrotic lung diseases such as idiopathic pulmonary fibrosis (29%), familial pulmonary fibrosis, drug- or toxin-induced lung disease, occupational lung disease, sarcoidosis, limited scleroderma, lymphangioleiomyomatosis, eosinophilic granuloma, and other disorders resulting in end-stage fibrotic lung disease [1].

The most frequent indications for bilateral lung transplantation (BLT) are suppurative pulmonary lung disease, cystic fibrosis and bronchiectasis (31%) and severe chronic obstructive pulmonary disease (COPD) resulting from tobacco use (26%), or α_1-antitrypsin deficiency (8%). In addition, more than 90% of transplant centers prefer to perform BLT when patients have idiopathic pulmonary hypertension (5%) [1].

Heart–lung transplantation (HLT) is performed at only a few transplantation centers and should be reserved for patients who cannot be treated by LT alone. The most frequent indications for HLT are Eisenmenger syndrome with a cardiac anomaly that cannot be corrected surgically and severe end-stage lung disease with concurrent severe heart disease. HLT is discussed in more detail in Chapter 183.

GUIDELINES FOR RECIPIENT SELECTION

There has been a revision of the original consensus-based guidelines for the selection of lung transplant candidates [2]. Any patient with end-stage pulmonary or cardiopulmonary disease with the capacity for rehabilitation can be considered for transplantation. The patient should have untreatable end-stage pulmonary disease, no other significant medical illness, have a limited life expectancy, and be psychologically stable and compliant.

Age

The 2006 international guidelines for the selection of transplant candidates [2] now suggest an age limit of 65 years regardless of procedure type. Although this is somewhat arbitrary, numerous patients with end-stage pulmonary disease are young to middle-aged, and there is a relative lack of available donors.

Relative Contraindications

Transplantation is not contraindicated in patients with systemic diseases that are limited to the lungs such as scleroderma, systemic lupus erythematosus, polymyositis, and rheumatoid arthritis. These cases should be considered on an individual basis. Osteoporosis has become a significant problem in the post-transplant period, and preexisting symptomatic osteoporosis has also been identified as a relative contraindication to transplantation.

Patients with active sites of infection are not considered to be good transplant candidates. Treated tuberculosis and fungal disease pose a particular problem but are not contraindications for LT. Many centers will not consider performing a transplant in a patient who is chronically colonized with a resistant organism (e.g., *Burkholderia species*, methicillin-resistant Staphylococcus, atypical mycobacterium, or Aspergillus) and it is recommended to try to eradicate these organisms in the pre-transplant period and to consider each patient on an individual basis. However, if considered, these patients should be candidates only for BLT procedures since the remaining colonized

lung could pose a serious threat to the new graft in the case of an SLT. This issue is of particular concern in cystic fibrosis patients who are often infected with drug resistant organisms. Both *Burkholderia cenocepacia* (specific strains) and *Burkholderia gladioli* are of concern due to poor posttransplant outcomes [3].

A requirement for invasive mechanical ventilation is a strong relative contraindication to transplantation, although LT has been performed successfully in small numbers of mechanically ventilated patients with CF, and other end-stage lung disease [4,5]. In one small series there was a longer time on postoperative mechanical ventilation and a longer ICU stay following LT. Rates of PGD, survival, and total hospital stay were similar to those in patients undergoing LT not on mechanical ventilation [4]. Recently venoarterial extracorporeal membrane oxygenation (ECMO) has been used in end-stage lung disease patients during transplantation with good short-term function and survival rates [5]. In a large review of the United Network Organ sharing (UNOS) database of patients undergoing LT on mechanical respiratory support 586 on mechanical ventilation and 51 on ECMO as a bridge to LT, the authors found that patients on mechanical ventilation or ECMO have lower survival rates following LT compared to those not requiring support [6]. Noninvasive ventilatory support is not considered a relative contraindication to transplantation

To be considered for transplantation, patients should have an ideal body weight of > 70% or ≤ 130% predicted (BMI 18 to 30 kg per m^2). Those patients with poor nutritional status may be too weak to withstand the surgical procedure; those patients who are obese make more difficult surgical candidates and may have higher mortality rates than nonobese patients.

Pretransplant low-dose therapy with corticosteroids has been proven to be acceptable for patients who cannot have therapy with corticosteroids completely discontinued. Initial data implicated corticosteroids as a cause of tracheal bronchial dehiscence. Currently, transplant programs will consider patients who can be maintained in the long term on a regimen of prednisone of ≤ 20 mg per day and may consider patients who are receiving higher doses.

Prior thoracotomy or pleurodesis was once considered to be a relative contraindication to transplantation due to increased technical difficulties and increased bleeding. Despite this, transplantation can be successfully performed in these patients.

Absolute Contraindications

The 2006 international guidelines [2] identified several absolute contraindications to LT including major organ dysfunction (i.e., renal creatinine clearance of ≤ 50 mg per mL per minute), HIV infection, hepatitis B antigen positivity, and hepatitis C with biopsy-documented liver disease. Active malignancy within the prior 2 years is also a contraindication to transplantation. For patients with a history of breast cancer greater than stage 2, colon cancer greater than Duke A stage, renal carcinoma, or melanoma greater than or equal to level 2, the waiting period should be at least 5 years. Restaging is suggested prior to transplant listing.

Severe nonosteoporotic skeletal disease, such as kyphoscoliosis, is often an absolute contraindication to transplantation, primarily because of the technical difficulties encountered during surgery.

Drug abuse and alcoholism are considered to be contraindications to transplantation because patients with these conditions are at high risk for noncompliance. Patients who continue to smoke despite having end-stage pulmonary disease are not candidates for LT. Transplant centers require patients to abstain from cigarette smoking, alcohol use, or narcotics use for 6 months to 2 years before being considered for lung transplant evaluation.

The patient must be well motivated and emotionally stable to withstand the extreme stress of the pretransplant and perioperative period. A history of noncompliance or significant psychiatric illness is an absolute contraindication

DONOR ALLOCATION AND SELECTION

Until the spring of 2005, as established by the United Network of Organ Sharing, lungs were allocated primarily by time on the waiting list, and not by necessity. In the spring of 2005, the system for donor allocation for lungs was revised, and assigned priority for lung offers became based on a benefit or need-based Lung Allocation Score [7]. The LAS is calculated using the following measures: (1) waitlist urgency measure (i.e., the expected number of days lived without a transplant during an additional year on the waitlist); (2) posttransplant survival measure (i.e., the expected number of days lived during the first year posttransplant); and (3) the transplant benefit measure (i.e., the posttransplant survival measure minus waitlist urgency measure) [8]. Although it is still too early to determine the long-term effects that this new allocation system will have on LT, it appears that many of the goals of the system (decreased waiting list deaths, and times, prioritizing patients by urgency rather than time on the list) are being accomplished, with comparable survival rates except in those with the very high LAS scores (> 46 in one study) [9,10]. There appears to be a stepwise decline in posttransplant survival as the LAS score increases. In patients with high LAS scores there was also higher morbidity including requirements for dialysis, infections, and longer lengths of stay [11]. Since the implementation of the LAS, the distribution of patient diagnoses on the list, and those transplanted, has also shifted from a majority of COPD patients to an increasing number of patients with pulmonary fibrosis. In addition, sicker patients are being transplanted.

Donor lungs are first distributed locally, then regionally, and finally nationally. Currently, the average time spent on the waiting list is approximately 18 to 24 months, and therefore close management of the listed transplant patient is required. Despite this close attention, a small percentage of patients die while awaiting transplantation.

A shortage of donor organs remains the primary factor limiting the number of LTs performed. Contributing to this shortage is the estimate that lungs for transplantation are procured from only 19% of multiorgan donors [12]. The vast majority of transplanted lungs are from brain-dead donors. A small number of LT procedures involving living related donors and non–heart-beating lung donors (also called donation after cardiac death [DCD]) have been performed at institutions specializing in these procedures [13]. In a small group of DCD donors lung transplant recipients, rates of PGD, acute rejection, bronchiolitis obliterans, and 2-year survival rates were comparable to those of lung transplant recipients from cadaveric donors during the same period. Graft function was better preserved in the DCD recipients [14].

The usual donor selection criteria are age younger than 60 to 65 years, no history of clinically significant lung disease, normal results from a sputum Gram stain, and a limited history of smoking (less than 20 pack-years). In addition, the lung fields should be clear as demonstrated by chest radiograph, and gas exchange should be adequate as demonstrated by a partial pressure of arterial oxygen (PaO_2) more than 300 mm Hg, while receiving fractional inspired oxygen (FIO_2) equal to 1, or a PaO_2/FIO_2 ratio of more than 300 with a positive end expiratory pressure (PEEP) of 5 cm H_2O. Bronchoscopy is also

part of the evaluation of the donor. The main goal of the endobronchial evaluation is to rule out gross aspiration or purulent secretions in the distal airways.

Lungs from extended donors (i.e., those who do not meet all of the criteria listed earlier) are now more frequently being transplanted in an attempt to expand the donor pool [15–18], and some centers are actively engaged in developing protocols for optimizing marginal donor lungs, thereby rendering them transplantable. By instituting a protocol including educational and donor management interventions, and changing donor classification and selection criteria, a single-organ procurement organization was able to increase the percentage of lungs procured from 11.5% to 22.5% with an increase in the number of procedures performed, without adverse recipient outcomes [15].

Donors are excluded from potential lung donation if there is evidence of active infection, human immunodeficiency virus, hepatitis, or malignancy. Donor and recipient compatibility is assessed by matching A, B, and O blood types and chest wall size. Human leukocyte antigen (HLA) matching is not routinely performed in LT except in patients with history of preformed donor-specific antibodies.

SURGICAL TECHNIQUES

Initially, double-lung transplantation was the procedure of choice; the anastomosis was placed at the level of the trachea. However, the rate of ischemic airway complications was prohibitive. Now, SLT or BLT (essentially sequential SLT) with anastomoses at the level of the mainstem bronchi is the preferred surgical technique. At the time of cardiac harvest, the donor lung is usually removed through a median sternotomy. The pulmonary veins are detached from the heart with a residual 5-mm cuff of left atrium. The pulmonary artery is transected from the main pulmonary trunk, and the mainstem bronchus is transected between two staple lines. During transportation to the recipient site, the partially inflated donor lung graft is placed into preservation solution, usually a low-potassium dextran solution with extracellular electrolyte composition or a modified Euro-Collins solution with an intracellular electrolyte composition at 4°C.

For SLT, the recipient surgery is performed through a posterolateral thoracotomy or sternotomy, or vertical axillary muscle-sparing minithoracotomy. Most centers start with the bronchial anastomosis, without a vascular anastomosis of the bronchial circulation of the recipient and donor lungs. Initially, most transplant procedures involved an end-to-end anastomosis, which was wrapped with a piece of omentum or pericardial fat with an intact vascular pedicle for assistance in bronchial revascularization. Subsequently, a telescoping technique was recommended, with the recipient and donor bronchi overlapping by approximately one cartilaginous ring. This procedure allowed the recipient's intact bronchial circulation to supply the donor bronchus. More recently, most anastomoses are performed with an end-to-end single suture in the membranous portion and a single or continuous suture in the cartilaginous portion, without omental wrap, and telescoping is performed when the donor and recipient bronchi differ in size and there is a natural, unforced telescoping of both bronchi [19,20].

After the bronchial anastomosis has been performed, the donor pulmonary veins are anastomosed end-to-end to the recipient's left atrium, and the pulmonary arteries are attached with an end-to-end anastomosis.

BLT is usually performed through a transverse thoracosternotomy (clamshell incision) or a median sternotomy followed by sequential single-lung procedures. Cardiopulmonary bypass may be required for patients with pulmonary hypertension or those who cannot tolerate single-lung ventilation or perfusion and who experience marked hypoxemia or hemodynamic instability. Although center specific, an increasing number of cases (nearly 50% of LT procedures at some institutions) are performed with the use of cardiopulmonary bypass.

GENERAL POSTOPERATIVE MANAGEMENT

After LT, patients usually remain intubated, require mechanical ventilation, and are transferred to the ICU. Most patients are ventilated in a volume-control mode, although in recent years some transplant centers have changed to pressure-control ventilation, or airway pressure release ventilation. In general, low tidal volume ventilation strategies are used. Airway pressures are kept as low as possible so that barotrauma and anastomotic dehiscence can be avoided. Many institutions use routine pharmacologic sedation. Patients are generally maintained with tidal volumes of 6 to 8 mL per kg postoperatively. At most institutions, a low level of PEEP (5.0 to 7.5 cm H_2O) is applied immediately after lung expansion in the operating room and is continued after transplantation. Early extubation is one of the main goals after LT, and lung transplant recipients who do not experience complications are extubated within the first 12 to 24 hours postoperatively if they meet the commonly accepted weaning criteria. Some centers may attempt to extubate immediately postoperatively [21]. Both postural drainage and chest physiotherapy can be routinely employed without concern for mechanical complications at the anastomosis, and patients should perform incentive spirometry soon after extubation.

Certain patient populations require special ventilator management. Most patients with idiopathic pulmonary hypertension undergo BLT; however, at a few centers some patients undergo SLT for pulmonary hypertension with an increased risk of reperfusion pulmonary edema because nearly all of the perfusion is going to the newly implanted lung.

Patients with obstructive lung disease can encounter problems if the delivered tidal volume or the required levels of PEEP are high. Occasionally, clinically significant acute native lung hyperinflation can occur and can compromise the newly transplanted lung and lead to hypotension and hemodynamic instability. To reduce this problem, some transplant centers avoid PEEP for patients undergoing SLT for obstructive disease. However, the problem is magnified when patients experience reperfusion injury or pneumonia after transplantation; in such cases the compliance of the transplanted lung is decreased and higher PEEP is required for maintaining oxygenation. As a consequence, the more compliant emphysematous lung becomes overexpanded and can herniate toward the contralateral hemithorax [22]. Attempts to prevent this possible complication by using selective independent ventilation with a double-lumen endotracheal tube have been tried. Lung hyperinflation is associated with a significantly longer stay in the intensive care unit (ICU), a longer duration of mechanical ventilation, and a trend toward higher mortality [23].

Pain control is usually provided by opiates, usually fentanyl, administered intravenously or morphine sulfate via an epidural catheter with a patient-regulated pain-control system.

Because many patients are nutritionally depleted before transplantation as a result of their underlying disease, postoperative nutrition is important. Ideally, enteral nutrition should be provided as soon as tolerated.

Antibiotics are routinely administered for the first 48 to 72 hours after transplantation. Antibiotic regimens include broad-spectrum antibiotic coverage for both Gram-negative

and Gram-positive bacteria. Most centers advocate empiric anaerobic coverage. Gram stains and cultures of sputum from the donor and the recipient may be used when available to guide the choice of appropriate antibiotics. Many centers routinely use antifungal agents such as inhaled amphotericin B, voriconazole, or itraconazole postoperatively. Most transplantation programs administer ganciclovir and, more recently, valganciclovir for CMV prophylaxis if either the patient or the donor is CMV-positive before surgery.

Immunosuppression is begun preoperatively with tacrolimus or cyclosporine and corticosteroids. Corticosteroids are administered in the operating room as intravenous methylprednisolone 0.5 to 1 g (usually administered at the time of reperfusion) and then at doses of 1 to 3 mg per kg daily for the next 3 days, followed by 0.8 mg per kg daily and then conversion to an equivalent oral dose. In the past, lympholytic medications, such as intravenous antithymocyte globulin (ATG) at 1.5 mg per kg daily for 3 to 5 days or muromonab-CD3 (Orthoclone OKT3) at 5 mg per day for the first 5 to 10 days, were used as induction therapy after transplantation; however, more recently the use of these medications has been limited. Some centers currently use interleukin (IL)-2 receptor blockers (e.g., basiliximab) for induction. A retrospective registry analysis of the impact of induction therapy on survival following LT showed a survival advantage with the use of interleukin-2- receptor antagonists in both SLT and BLT recipients and in BLT recipients treated with ATG [24]. After the transplantation procedure, most patients begin a triple immunosuppression protocol with a combination of prednisone, a calcineurin agent, tacrolimus or cyclosporine, and a cell cycle inhibiting agent, mycophenolate mofetil or azathioprine [25].

POSTOPERATIVE PROBLEMS

Primary Graft Dysfunction

Perhaps the most serious problem in the postoperative period after LT is PGD [26]. It is estimated that as many as 80% of patients will experience some degree of PGD and as many as 15% of cases can be severe [27]. A 2005 consensus conference attempted to standardize the grading of PGD on the basis of gas exchange and the presence of radiographic infiltrates (Table 189.2). When the acute lung injury definition of acute respiratory distress syndrome (ARDS)—a PaO_2/FIO_2 ratio of less than 200 is used to define the most severe form of PGD (grade 3), the reported incidence is 10% to 25%. PGD

TABLE 189.2

GRADING OF THE SEVERITY OF PRIMARY GRAFT DYSFUNCTION

Grade	PaO_2/FIO_2	Radiographic infiltrates consistent with pulmonary edema
0	> 300	No
1	> 300	Yes
2	200–300	Yes
3	< 200	Yes

Adapted from Christie JD, Carby M, Bag R, et al: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 24(10):1454–1459, 2005, with permission.

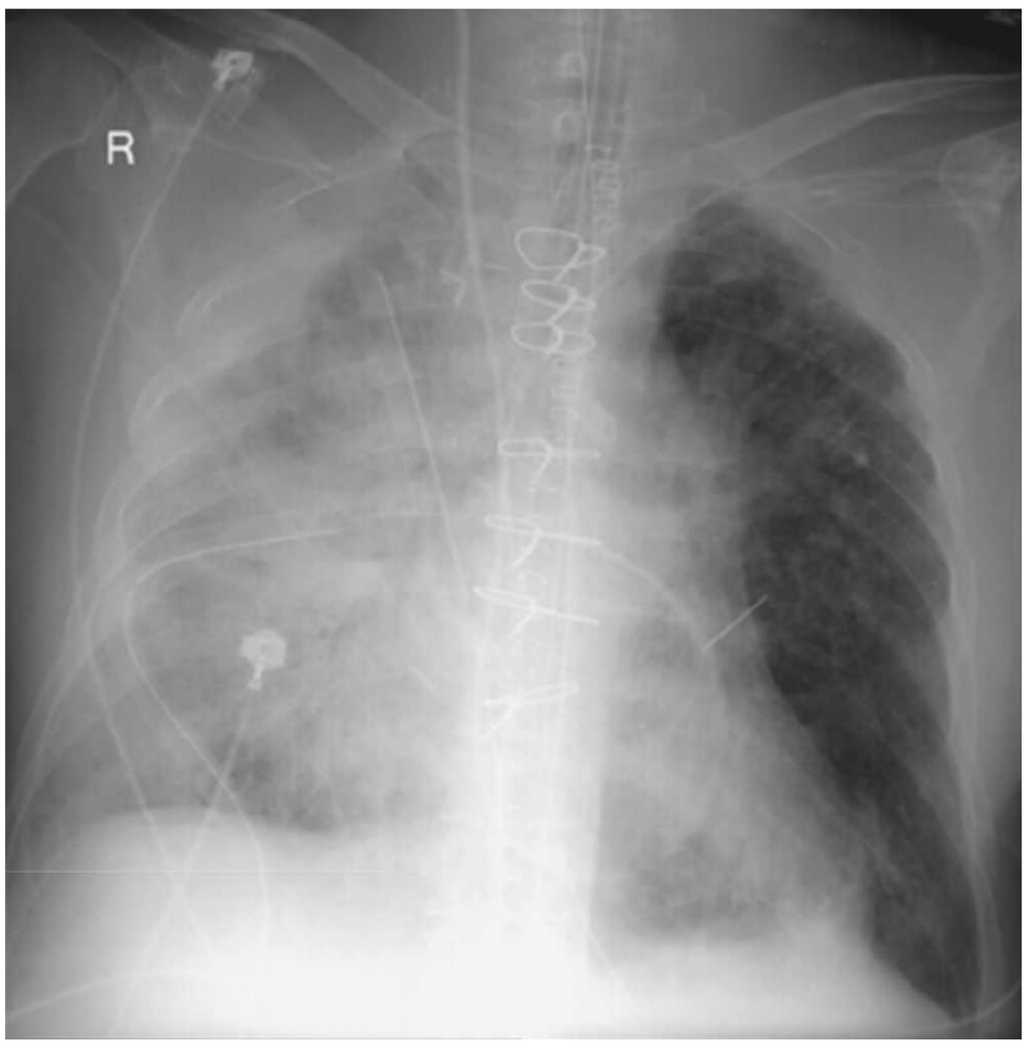

FIGURE 189.1. Severe primary graft dysfunction in the transplanted lung following a right single-lung transplant for idiopathic pulmonary fibrosis.

is a diagnosis of exclusion; the condition usually occurs hours to 3 days after LT, whereas rejection and infection are more common after the first 24 hours. A stenosis at the venous anastomosis presents with similar signs and symptoms, but this diagnosis can be excluded by transesophageal echocardiography. However, because the timing of these disorders may vary, differentiation may be difficult [26].

PGD can persist to various degrees for hours to days after LT. Clinically, PGD is characterized by the appearance of new alveolar or interstitial infiltrates on radiographs, a decrease in pulmonary compliance, an increase in pulmonary vascular resistance, and a disruption in gas exchange. Radiographic findings in these patients include a perihilar haze, patchy alveolar consolidations, and, in the most severe form, dense perihilar and basilar alveolar consolidations on air bronchograms (Fig. 189.1). Pathology reports from biopsy specimens, autopsies, or lung explants removed during retransplantation indicate diffuse alveolar damage. PGD usually stabilizes over the next 2 to 4 days and then begins to resolve, or worsens with all cause mortality rates at 30 days exceeding 40% in some studies.

PGD is managed supportively with diuretics and mechanical ventilation, often with protective ventilatory strategies [28]. Because endogenous nitric oxide (NO) activity decreases after LT, there are several reports of the successful use of inhaled NO for hypoxemia and for pulmonary hypertension as a consequence of graft dysfunction after transplantation [29–32]. However, in one randomized, placebo-controlled trial (84 patients), the prophylactic inhalation of NO 10 minutes after reperfusion and for a minimum of 6 hours, was not shown to be beneficial for hemodynamic variables, reperfusion injury, oxygenation, time to extubation, length of intensive care or hospital stay, or 30-day mortality [31]. A similar study beginning NO at the onset of ventilation supported these findings [30]. The use of artificial surfactant replacement has also been examined [33–35]. An open randomized prospective trial studying the use of instilled bovine surfactant immediately after establishment of the bronchial anastomosis, showed improved oxygenation and decreased PGD, shortened intubation time, and enhanced

TABLE 189.3

POSSIBLE RISK FACTORS FOR PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

Recipient characteristics
Pulmonary hypertension
Diffuse parenchymal lung disease diagnosis
Body mass index > 25 kg/m^2
Operative factors
Cardiopulmonary bypass during surgery
Prolonged ischemic time for the organ
Methods/techniques of preservation and reperfusion
Blood product transfusions
Donor characteristics
Female gender
African American race
Age < 21 y or > 45 y
Prolonged mechanical ventilation
Aspiration pneumonia
History of tobacco use
Trauma
Hemodynamic instability after brain death

Adapted from references [27,43–48].

early post-LT recovery in the treatment group, although an unusually high incidence of PGD was found in the control group [34]. The use of ECMO for severe early graft dysfunction [36] has also been described, with a hospital survival rate of 42% in an analysis of the Extracorporeal Life Support Organization registry study [37]. High-frequency oscillatory ventilation and independent lung ventilation have been used in some cases. Retransplantation has also been performed, but the outcome for patients undergoing retransplantation for PGD has been very poor.

Severe PGD usually leads to compromised short-term outcomes, including increase in the duration of mechanical ventilation and lengths of stay, poor 1-year survival rates (40% for patients with PGD in one single-center study), and compromised function among survivors [38,39]. Long-term outcomes, such as pulmonary function and the incidence of bronchiolitis obliterans, are also impacted, and more severe PGD and longer duration of PGD significantly increases the development of bronchiolitis obliterans syndrome (BOS) [40,41].

Although the mechanisms of PGD have not been completely delineated, several contributing factors have been postulated, including the disruption of lymphatics, bronchial vasculature, or nerves, and lung injury occurring either during preservation of the graft or after reperfusion [42]. Multiple risk factors (Table 189.3) may be associated with the development of PGD [27,43–48]. Some have borne out in multivariate analysis. Donor variables include: female gender, African American race, donor age less than 21 years and more than 45 years, prolonged mechanical ventilation, aspiration pneumonia, history of tobacco use, trauma, and hemodynamic instability following brain death. The technique used for graft preservation and the perfusion solution (e.g., Eurocollins), the use of cardiopulmonary bypass, prolonged ischemic times, and blood product transfusions may also be risk factors for PGD. Recipient factors contributing to PGD include: a diagnosis of pulmonary hypertension, elevated pulmonary artery pressures at the time of transplant, body mass index (BMI) > 25 kg per m^2, and diffuse parenchymal lung disease. Humoral rejection has recently been postulated to be a risk factor for PGD [48]. Since the institution of the LAS, some studies have shown an increase in the incidence of PGD [49] but others have not supported this finding [50].

Intensive Care Unit Outcomes

Few data are available for predicting outcomes and length of ICU stay after LT. It is known that the duration of mechanical ventilation is prolonged and the ICU mortality increased for patients who experience PGD [38]. One study found that an immediate postoperative PaO_2/FIO_2 ratio of less than 200 predicted an ICU stay of 5 days or more [51]. In another study, poor nutritional status (BMI below the 25th percentile) in patients remaining in the ICU for more than 5 days was associated with a higher ICU mortality rate [52]. In this same study, a preoperative diagnosis of pulmonary hypertension or restrictive lung disease and BLT rather than SLT were associated with longer ICU stays. Another study examined the value of intravascular volume status and central venous pressure (CVP) in predicting ICU outcomes; the results indicated that a CVP higher than 7 mm Hg after transplantation was associated with a longer duration of mechanical ventilation, longer ICU and hospital stays, and higher 2-month mortality rates [53].

Among patients requiring prolonged ICU stays, those who underwent tracheostomy were more likely to have undergone BLT, to have required cardiopulmonary bypass during the procedure, to have experienced postoperative pneumonia, to have had more significant reperfusion injury at 48 hours, to have had longer initial periods of mechanical ventilation, and to have required reintubation more often [54].

Late Complications Requiring Admission to the Intensive Care Unit

The number of lung transplant recipients who are admitted to the ICU is expected to increase as the number of long-term survivors increases. The postoperative mortality rate has decreased because of improved surgical techniques and perioperative care, and approximately 90% to 95% of patients are discharged alive after transplantation. However, after this immediate posttransplantation period, lung transplant recipients are more likely than some other solid-organ transplant recipients to experience infection or rejection that often requires readmission to the ICU.

Nearly 25% of lung transplant recipients require an ICU admission after the initial hospital discharge. The most common admission diagnoses are respiratory failure and sepsis. These patients frequently require mechanical ventilation (53%), and the mortality rate is generally close to 40%. Prognostic factors for mortality include higher acute physiology and chronic health evaluation (APACHE) scores, a forced expiratory volume in one second (FEV_1) lower than the patient's best posttransplantation FEV_1, nonpulmonary organ dysfunction, low-serum albumin level, and longer duration of mechanical ventilation [55]. Patients admitted with a diagnosis of BOS who require mechanical ventilation are at the highest risk of mortality. The long-term survival of patients who recover from the ICU stay is also compromised; however, a high percentage of patients (50%) can still enjoy long-term survival after an ICU admission.

Airway Complications

Because of the lack of revascularization of the bronchial circulation, anastomotic complications, such as bronchial

dehiscence, bronchial stenosis, and bronchial infection, are the main airway complications reported in the first few weeks to months after LT. The incidence of anastomotic complications has decreased as surgical techniques have improved and surgeons have gained experience with the procedure. The reported incidence of this complication ranges widely: some studies report it to be as high as 33%; others, as low as 1.6%. However, in reality, most recent series suggest a range of 7% to 18% [56], with a related mortality rate of 2% to 4%. Risk factors for airway complications include ischemia of the donor bronchus during the posttransplant period, due to loss of bronchial blood flow (only the pulmonary vessels are revascularized during LT surgery), surgical techniques for the anastomosis, length of the donor bronchi, acute rejection, and bronchial infections.

Airway complications can be classified as early or late. Early airway complications usually occur during the first 4 to 12 weeks after transplantation and manifest themselves as a partial or complete anastomotic dehiscence or a fungal (usually *Aspergillus* or *Candida* species) or bacterial (usually *Staphylococcus* or *Pseudomonas* species) anastomotic infection. These conditions can subsequently result in anastomotic strictures or bronchomalacia. Clinically, bronchial dehiscence may cause prolonged air leaks in the early posttransplantation period. In some cases, the dehiscence may also lead to infection or the formation of peribronchial abscesses or fistulas. The results of chest radiographs and computed tomography (CT) scans are usually nonspecific; however, the appearance of extraluminal air on chest CT scans is very sensitive and specific for the diagnosis of anastomotic dehiscence. Bronchoscopy is the preferred diagnostic method for evaluating the bronchial anastomosis. This procedure may be performed routinely (surveillance bronchoscopy) or because of pulmonary symptoms, usually during the first 6 months after transplantation. During this period, the anastomosis should be evaluated carefully, the integrity of the mucosa should be assessed, and specimens from a bronchial wash or brush should be sent for cultures and cytologic examination. If there is any evidence of infection, antibiotics and antifungals (usually inhaled amphotericin with or without itraconazole or voriconazole) should be administered based on culture results.

Late bronchial anastomotic complications, including stenosis (most common), bronchomalacia, and development of exophytic granulation tissue are often the result of infection or dehiscence during the early weeks after transplantation. These complications manifest themselves as cough, shortness of breath, wheezing, dyspnea on exertion, and worsening obstruction as documented by pulmonary function testing. The characteristic flow volume loop demonstrates a concave appearance in both the inspiratory loop and the expiratory loop. Bronchial strictures or stenoses may also be seen on chest radiographs or CT scans, or by bronchoscopy. Therapeutic options for anastomotic complications include balloon dilation of a stricture, stent placement, cryotherapy, argon beam coagulation, laser procedures, and, rarely, surgery.

Rejection

Graft rejection is categorized clinically according to the time of onset after transplantation and the histopathologic pattern. The three types of rejection are hyperacute, acute, and chronic. Hyperacute rejection is mediated by preexisting alloantibodies that immediately bind to the donor vascular epithelium and lead to vessel thrombosis because of complement activation. This was thought to be a rare complication after LT. However, humoral or antibody mediated rejection is currently an area of active research in the field of LT [57]. Humoral rejection is characterized by local complement activation or the presence of antibody to donor HLAs and may be a risk factor for BOS. Treatment of humoral rejection includes plasmapheresis, intravenous immunoglobulin and/or rituximab, a monoclonal antibody against the CD-20 antigen.

Acute Rejection

As many as 50% to 55% of patients experience acute rejection during the first postoperative month, and as many as 90% will experience at least one episode of acute rejection within the first year [57]. Acute rejection usually occurs between 10 and 90 days after LT. It is not uncommon (20% of lung transplant recipients) for a single patient to experience either recurrent (more than two episodes) and/or persistent (failure to resolve with standard therapy) rejection. Acute rejection usually does not occur as frequently after the first postoperative year. Risk factors for acute rejection are poorly defined, but HLA mismatches may be correlated with its occurrence.

Clinically, acute rejection manifests itself as cough, shortness of breath, malaise, and fever. Occasionally, the presentation is asymptomatic; 68% of transplantation centers advocate surveillance bronchoscopy for the detection of this condition, although outcome data are not available [25]. Physical examination may detect rales or wheezing. The usefulness of chest radiography depends on the time since transplantation. Typically, during the first month the results of chest radiography can be abnormal in as many as 75% of rejection episodes; however, the results of radiography are abnormal in only 25% of rejection episodes that occur more than 1 month after transplantation. The most common radiographic patterns associated with acute rejection are a perihilar flare, and alveolar or interstitial localized or diffuse infiltrates with or without associated pleural effusion. In addition, CT may show ground glass opacities, septal thickening, and volume loss. New pleural fluid or increases in the amount of pleural fluid produced during the second to sixth week after LT is common among patients with acute lung rejection. The characteristics of the fluid are consistent with those of an exudate: the total lymphocyte count is often more than 80% of the total number of white blood cells.

Physiologic findings during periods of acute rejection include hypoxemia and deterioration in pulmonary function. Pulmonary function abnormalities are characterized by at least a 10% to 15% decline in FEV_1 from baseline and/or at least a 20% decline in forced expiratory flow (FEF) over 25% to 75% of expired vital capacity. Once again, these changes are nonspecific and can also be seen with infectious processes and graft complications.

Because clinical criteria alone cannot differentiate acute rejection from infection and less common graft complications, transbronchial biopsy (TBBx) with BAL has become the primary diagnostic procedure. The sensitivity of diagnosing acute rejection by TBBx ranges from 61% to 94%, and the specificity ranges from 90% to 100%. A histologic grading system for acute pulmonary rejection was proposed in 1990 and revised in 1996 and 2007 [58]. Pathologically, acute rejection is characterized by perivascular, mononuclear lymphocytic infiltrates with or without airway inflammation; histologically, it is graded from A_0 to A_4 on the basis of the degree of perivascular inflammation. In addition, the airway can be involved by lymphocytic bronchitis or bronchiolitis, which is graded from B_0 to B_x [58]. As rejection progresses, the perivascular lymphocytic infiltrates surrounding the venules and arterioles become dense and extend into the perivascular and peribronchiolar alveolar septa. Severe rejection may involve the alveolar space; parenchymal necrosis, hyaline membranes, and necrotizing vasculitis have been described [58]; and respiratory failure requiring mechanical ventilation can occur.

Once acute rejection has been diagnosed, treatment consists of augmenting the level of immunosuppression. Intravenous methylprednisolone (10 to 15 mg per kg daily for 3 days)

followed by an increase in the maintenance regimen of prednisone regimen to 0.5 to 1 mg per kg daily, with tapering over the next several weeks, is a standard treatment regimen. Maintenance immunosuppression should also be augmented. Typically, symptoms resolve in days, and histologic follow-up 3 to 4 weeks later should demonstrate resolution. Recurrent or persistent acute rejection may require conversion in the baseline immunosuppressive regimen. Lympholytic therapy, methotrexate, photophoresis, total lymphoid irradiation, and aerosolized cyclosporine have been used with varied success [59].

Obliterative Bronchiolitis

Chronic rejection has been equated with the histologic finding of obliterative bronchiolitis (OB); it is a primary cause of morbidity and mortality after LT and the leading single cause of death more than 1 year after transplantation [1]. The incidence of OB ranges from 35% to 50% at various centers. OB has been defined clinically by an obstructive functional defect and histologically by obliteration of terminal bronchioles. OB generally occurs in a mean of 16 to 20 months after LT, but it has been reported as early as 3 months after transplantation. More than 50% of recipients will experience some degree of OB by 5 years after transplantation [1].

The causes of and risk factors for OB remain unclear. Several possible causes have been proposed, including uncontrolled acute rejection, lymphocytic bronchiolitis, CMV pneumonitis, CMV infection without pneumonitis, community acquired respiratory viruses, gastroesophageal reflux disease, PGD, antibody-mediated rejection, HLA-A mismatches, total HLA mismatches, absence of donor antigen-specific hyporeactivity, non-CMV infection, older donor age, and bronchiolitis obliterans with organizing pneumonia [40,41,60–63]. The most consistently identified risk factor is acute rejection, particularly in those patients who experience recurrent, high-grade episodes of acute rejection.

Clinically, OB can manifest itself as an upper respiratory tract infection and can be mistakenly treated as such. Other patients exhibit no clinical symptoms, but pulmonary function testing demonstrates gradual obstructive dysfunction. FEV_1 has been the standard spirometric parameter used for diagnosis, but midexpiratory flow rates may be a more sensitive parameter for early detection.

Typically, chest radiographs are not helpful in the diagnosis of OB because their results are unchanged from the results of baseline posttransplantation radiographs. High-resolution CT scans may show peripheral bronchiectasis, patchy consolidation, decreased peripheral vascular markings, air trapping, mosaicism, tree-in-bud changes, and bronchial dilation; these findings may aid in the diagnosis of OB [64]. Air trapping on end-expiratory high-resolution CT scans has been shown to be a sensitive (91%) and accurate (86%) radiologic indicator of OB, but it may not be able to provide an early diagnosis of this disorder. As with acute rejection, TBBx is used to diagnose OB, but primarily to exclude other diagnoses. The classic pathologic finding is constrictive bronchiolitis. Unfortunately, the sensitivity of TBBx for diagnosing OB is low (range: 15% to 87%), and the diagnosis of OB is often made by exclusion. OB is graded physiologically on the basis of the degree of change in pulmonary function (FEV_1) from baseline [61,62]. Because of the variability in obtaining bronchioles by TBBx, the ISHLT has established a staging system for BOS [62]. This staging is based on a reduction in FEV_1 of more than 20% from baseline after transplantation and is associated with a decrease in the FEF 25% to 75%, with or without the pathologic documentation of OB.

Once OB has been diagnosed histologically or clinically by excluding alternative diagnoses, treatment involves administering high-dose methylprednisolone followed by a tapering course of oral corticosteroids. Lympholytic depleting agents such as ATG, OKT_3, alemtuzumab, and basiliximab can be considered if there is no clinical response to corticosteroid treatment. Therapy may stabilize pulmonary function, but it only rarely results in substantial improvement. Alternative immunosuppressants such as sirolimus have also been associated with stabilization of pulmonary function when used as rescue treatment for BOS. Methotrexate, total lymphoid radiation, aerosolized cyclosporine, photophoresis, and newer immunosuppressants have been used to treat refractory cases of OB. Inhaled cyclosporine may be added for cases of lymphocytic bronchiolitis. Several studies have shown stabilization and/or improvement in BOS when a macrolide agent, such as azithromycin or clarithromycin is added to the regimen, likely due to the immunomodulating effects [65–67].

Infection, including bronchiectasis, frequently complicates intensive immunosuppression for OB and may result in death. Pseudomonas is a common offender, and aerosolized aminoglycoside antibiotics or suppressive quinolone treatment may be considered. Because most cases of OB can only be stabilized, strategies directed at prevention, early diagnosis, and treatment are necessary for the preservation of lung function. Retransplantation has been performed with varied results. Survival rates are somewhat lower than those after the initial transplantation and are superior when performed for the indication of BOS (1 year 62% and 5 year 45%), than for PGD [68,69].

Infectious Complications

Infections are an important cause of early and late morbidity and mortality after transplantation and are the leading single specific cause of death during the first year after transplantation [1]. The incidence of infection is significantly higher among recipients of lung transplants than among recipients of most other solid organ transplants; this higher incidence may be related to the continuous exposure of the allograft to the environment. Other predisposing factors include a diminished cough reflex because of denervation, poor lymphatic drainage, decreased mucociliary clearance, recipient-harbored infection, and, occasionally, transfer of infection from the donor organ. Nosocomial infections, such as urinary tract infections, ventilator-assisted pneumonia, and infections at the site of the surgical wound or the vascular access, also occur during the early postoperative period. However, in most circumstances the allograft is the primary site of infection.

Bacterial Infections

Bacterial pneumonia is the most common life-threatening infection that develops during the early postoperative period. Its incidence during the first two postoperative weeks is reported to be as high as 35% [70–72]. Common organisms include *Pseudomonas aeruginosa* and *Staphylococcus species*. The incidence of perioperative bacterial pneumonia has been reduced to as low as 10% by prophylaxis with broad-spectrum antibiotics, usually an antipseudomonal cephalosporin and clindamycin, and by routine culture of the trachea of both the donor and the recipient at the time of transplantation. Prophylactic antibiotics are usually discontinued after 3 days if the results of cultures are negative; the antibiotics are tailored to the cultured organisms if the results are positive. For transplant recipients with bronchiectasis, postoperative bacterial prophylaxis is usually continued for 14 days. The incidence of bacterial pneumonia is high during the first 6 months after transplantation but decreases thereafter, although a second late peak in incidence often occurs when immunosuppression is augmented for the treatment of chronic rejection. During the early posttransplantation period, bacterial infection due to Staphylococcus or, less

commonly, Pseudomonas can develop at or distal to the site of the anastomosis.

It is often difficult to distinguish pneumonia from other early graft complications, such as reperfusion injury, pulmonary edema, rejection, and other causes of infection. In addition, differentiating between colonization and invasion may be difficult and often requires invasive procedures such as bronchoscopy with BAL, quantitative sterile brush sampling, or TBBx.

Other Infections

Atypical pneumonias, including those due to Legionella, mycobacteria, and Nocardia, are uncommon during the first month after transplantation but occur among 2% to 9% of recipients of lung or heart–lung transplants. At transplantation centers that routinely administer prophylaxis with trimethoprim–sulfamethoxazole during the first year after transplantation and reinitiate it when immunosuppression is augmented, the incidence of Pneumocystis pneumonia is less than 1%.

Most opportunistic infections occur within 6 months after transplantation. Sustained immunosuppression leading to a decrease in cell-mediated immunity predisposes the patient to infection with opportunistic organisms such as Aspergillus, Mycobacterium, Nocardia, and geographically endemic fungi.

Viral Infections

Viral infections are a primary cause of morbidity and mortality among long transplant recipients. During the first 6 months after transplantation, CMV accounts for most of the viral infections among these patients [72,73]. The typical time period for the development of CMV infection is 30 to 150 days postoperatively; the incidence of illness (i.e., infection and disease) is approximately 50%. Risk factors for CMV disease depend on the serology of the donor and the recipient and on the use of high-intensity immunosuppressive therapy, including cytolytic therapy. Approximately 15% to 35% of CMV-positive patients who receive grafts from either CMV-positive or CMV-negative donors experience CMV disease, whereas approximately 55% of CMV-negative patients who receive a graft from a CMV-positive donor may experience CMV disease. Most studies indicate that CMV pneumonitis contributes to the development of chronic rejection [62].

CMV can cause a wide spectrum of disease, ranging from asymptomatic infection, such as shedding of the virus in the urine or BAL, to widespread dissemination. The most common presentation of CMV among lung transplant recipients is pneumonitis, but the infection may also present as gastroenteritis, hepatitis, or colitis. CMV pneumonitis can often be confused with acute rejection. Clinical findings of CMV pneumonitis include fever, cough, flu-like illness, hypoxemia, an interstitial or alveolar infiltrate, and leukopenia. A definitive diagnosis of invasive disease requires cytologic or histologic changes in cell preparation or tissue. Therefore, diagnosis often requires flexible bronchoscopy with TBBx and BAL; this combination can detect 60% to 90% of CMV pneumonias. Currently, plasma-based polymerase chain reaction (PCR) assays are used to screen patients and to detect CMV infection [74]. The risk of CMV pneumonitis after LT is usually related to the serum concentration of CMV DNA, and this measure is used in many programs for the preemptive management of CMV [75].

The pathologic hallmark of CMV infection is a cytomegalic 250-nm cell containing a large central basophilic intranuclear inclusion. This inclusion is referred to as an "owl's eye" because it is separated from the nuclear membrane by a halo. Identifying CMV cytologically is very specific (98%) but lacks sensitivity (21%) for detecting the presence of infection. Other pathologic findings in the lung parenchyma of patients with CMV pneumonia include a lymphocytic and mononuclear-cell interstitial pneumonitis.

Ganciclovir (oral or intravenous) and oral valganciclovir are currently the mainstays of therapy for invasive CMV disease [73]. Bone marrow toxicity is one of the primary limiting side effects of ganciclovir therapy and may necessitate conversion to an alternative agent such as foscarnet. Most centers also use CMV-specific hyperimmunoglobulin to treat CMV disease.

Prophylaxis against CMV infections has become an important strategy at most transplantation centers. Initially, some centers attempted to match CMV-negative recipients with CMV-negative donors; however, the limited donor supply did not allow the continuation of this practice. The use of CMV-negative blood products is advocated. Prophylaxis with ganciclovir or valganciclovir seems to be effective in delaying the onset of CMV infection. Most centers give prophylaxis to all patients except CMV-negative recipients who receive grafts from CMV-negative donors. Prophylaxis is usually recommended for at least 90 days, particularly for CMV-negative recipients of grafts from CMV-positive donors. A recent randomized, controlled, multicenter study examined the efficacy of extending valganciclovir prophylaxis from the standard 3 months to 12 months in at risk (either donor or recipient CMV positive) patients. The investigators found a significant reduction in CMV infection, disease, and disease severity without increased ganciclovir resistance or toxicity in those patients receiving the longer course of therapy [76]. For patients at highest risk of infection, CMV hyperimmunoglobulin may be added to the regimen. Preemptive strategies, such as initiating treatment when a high level of CMV DNA is detected by PCR, may also delay and decrease the severity of CMV infection and may become the standard of care.

Other viruses that affect lung transplant recipients include herpes simplex virus (early after transplantation), community acquired respiratory viruses, such as respiratory syncytial virus, other paramyxoviruses (such as parainfluenza), influenza virus, metapneumovirus, and adenovirus [77]. Some transplantation programs initiate prophylaxis with acyclovir for herpes infection after the discontinuation of ganciclovir.

Fungal Infections

Fungal infections are more common among recipients of lung transplants than among recipients of other solid-organ transplants [78,79]. The overall incidence of invasive fungal infection after LT ranges from 15% to 35%. Such infections usually develop during the first few months after transplantation. Fungal infections carry the highest morbidity and mortality rates of all infections after transplantation; mortality rates can range from 40% to 70%.

Aspergillus species such as *A. fumigatus, A. flavus, A. terreus*, and *A. niger* can be colonizing organisms, can cause an infection that suggests an indolent, progressive pneumonia, or can cause an acute fulminant infection that disseminates rapidly. Aspergillus can invade blood vessels and may appear as an infarct on chest imaging or present with hemoptysis. The radiographic findings of pulmonary aspergillosis include focal lower-lobe infiltrates, patchy bronchopneumonic infiltrates, single or multiple nodules with or without cavitation, thin wall cavities, and opacification of the entire lung graft. High-resolution CT scans may reveal a halo sign that is believed to be pathognomonic for angioinvasive fungal infections such as aspergillosis [80]. Other manifestations of Aspergillus infection include pseudomembranous tracheobronchitis, often at and distal to the site of the anastomosis. Diagnosing invasive aspergillosis requires identifying organisms within tissues. These organisms can appear as septate hyphae that branch at acute angles and can be detected on hematoxylin-eosin and methenamine silver stains.

Survival rates for patients with Aspergillus infection have been improved by the early initiation of broad-spectrum azoles (such as voriconazole or itraconazole), high-dose amphotericin, or both, sometimes with the addition of an echinocandin, and a reduction in immunosuppressive therapy. Surgical resection may rarely be required to maximize cure rates in patients with aspergillosis. A lipid formulation of amphotericin B should also be considered for the management of invasive fungal infections among patients who cannot tolerate conventional amphotericin B or who experience nephrotoxicity with conventional amphotericin B, and among patients with progressive fungal infection despite therapy with conventional amphotericin. Prophylaxis with the azoles (voriconazole or itraconazole) for 3 to 6 months, and/or with amphotericin or aerosolized amphotericin, has shown promise in decreasing the incidence of Aspergillus infection after transplantation [81].

Candidal infections may occur during the early postoperative period but usually do not cause invasive disease. *Candida* species can cause a variety of syndromes among lung transplant recipients; these syndromes include mucocutaneous disease, line sepsis, wound infection, and, rarely, pulmonary involvement. Fluconazole and caspofungin have emerged as effective alternatives for treating infections caused by *Candida albicans*, but amphotericin B may still be considered for widespread disease. Fluconazole appears to be less active against other *Candida* species such as *C. glabrata* and *C. krusei*.

Less common causes of fungal infections among lung transplant recipients include *Cryptococcus neoformans* and the dimorphic fungi (*Coccidioides, Histoplasma*, and *Blastomyces*). Amphotericin B or the newer broad-spectrum azole agents are the initial therapeutic choices for treating serious infections with the invasive mycoses. The dose, duration of therapy, and alternative therapies differ depending on the organism.

Immunosuppression

After LT, a typical regimen for the maintenance of immunosuppression consists of tacrolimus at a dose of approximately 0.1 mg per kg orally every day in two divided doses (adjusted to maintain a serum concentration of 8 to 15 ng per mL), or cyclosporine 5 mg per kg orally every day in two divided doses (with dose adjusted to maintain serum concentrations of 250 to 350 ng per mL), and mycophenolate mofetil at a dose of 1 to 3 g daily, or azathioprine 1 to 2 mg per kg daily (adjusted to maintain a leukocyte count higher than 4,000 to 4,500 per mm^3), and prednisone approximately 0.5 mg per kg daily for the first month and then tapered by 5 mg per week over the next few months to a final maintenance dose of 5 mg per day. A minority of transplantation programs completely discontinue the administration of prednisone approximately 1 year after transplantation. The role of sirolimus after LT remains to be established. It is recommended that sirolimus not be used in the early perioperative period due to impaired wound healing.

Physicians caring for transplant recipients must be aware of the numerous drugs that can interact with tacrolimus and cyclosporine. For example, the azoles cause a significant increase in the serum concentrations of cyclosporine and tacrolimus. Likewise, discontinuing azole agents without increasing the dose of cyclosporine or tacrolimus can cause an acute and life-threatening decrease in the therapeutic concentrations of these drugs. Interactions with macrolide antibiotics, calcium channel blockers, and gastric motility drugs have also been reported. The concentrations of cyclosporine and tacrolimus are decreased by rifampin and anticonvulsants.

All immunosuppressants are associated with toxicity and drug interactions [82]. The details of these complications are discussed in a separate chapter.

Miscellaneous Complications

Another possible complication of LT is postoperative hemorrhage requiring reexploration. One of the early clues to this diagnosis is radiographic evidence of a hemothorax or what appears to be a retained clot, or a large volume of blood draining from the thoracostomy tubes. This complication may occur more frequently among patients who require cardiopulmonary bypass with its attendant requirement for anticoagulation or among patients with pleural adhesions from previous procedures such as pleurodesis or diagnostic or therapeutic lung surgery. Persistent air leaks can occasionally occur but are unlikely unless the bronchial anastomosis loses its integrity, because the lung parenchyma is normally not entered during a routine LT procedure [83].

In addition to the bronchial anastomotic complications discussed earlier, vascular anastomotic complications can occur. A stenosis at the venous anastomosis is indicated by radiographic evidence of pulmonary edema and infiltrates; this condition can be confused with PGD and is usually diagnosed by transesophageal echocardiography. A stenosis at the arterial anastomosis is suggested by unexplained gas exchange abnormalities and pulmonary hypertension.

Phrenic nerve dysfunction and diaphragmatic paralysis, which occur in conjunction with other types of cardiothoracic surgery, occur after LT with an incidence of 3% to 9.3% and are associated with a prolongation in the number of days for which mechanical ventilation is required, an increase in the length of stay in the ICU, an increase in the use of ICU resources, and an increase in the need for tracheostomy [84]. An inability to wean the patient from mechanical ventilation may indicate phrenic nerve dysfunction; the diagnosis can be confirmed by phrenic nerve conduction studies. For patients who do not require ventilation, the diagnosis of phrenic nerve dysfunction can be made with a fluoroscopic "sniff test." If the injury is the result of stretching of the phrenic nerve or trauma to the nerve during the surgical procedure but the nerve is not completely transected, a slow recovery can be anticipated. Complete transection is rare, but the damage is permanent. Diaphragmatic plication or pacing can be performed in some cases.

Pleural effusions can develop and/or persist following LT. The characteristics of these effusions are usually lymphocyte predominant exudates and can be associated early on with severing of the lymphatics (i.e., chylous effusion) or with rejection. A single-center study of a large number of lung transplant patients found that 27% of pleural effusions in these patients required drainage. 96% of the effusions were exudates, 27% of patient had infected pleural effusions with organisms such as fungal pathogens (specifically Candida most commonly), followed by bacterial etiologies. These infected effusions were characterized by high lactate dehydrogenase levels and neutrophilia [85]. Other causes of pleural effusions include heart failure, pulmonary embolism, and trapped lung. Rarely pleurodesis or decortication may be required.

Lung transplant recipients also experience gastroparesis, severe gastroesophageal reflux resulting in aspiration pneumonia, and an increased incidence of gastrointestinal emergencies [86]. These conditions include colonic perforation, small-bowel obstruction, diverticulitis, CMV colitis, megacolon, prolonged ileus, ischemic bowel, and pancreatitis [87]. Gastroesophageal reflux may be more severe among transplant recipients with cystic fibrosis.

Renal insufficiency is also a frequent complication among lung transplant recipients. This complication results from a combination of infections leading to sepsis and acute tubular necrosis, or from medication-related renal toxicity.

Cardiac arrhythmias, especially supraventricular arrhythmias such as atrial fibrillation, commonly develop in the perioperative period [88].

In one series of lung transplant recipients, the incidence of deep venous thrombosis and pulmonary embolism was reported to be 8.6%. This complication was believed to be related to alterations in coagulability leading to a hypercoagulable state or hypercoagulability due to their underlying disease [89,90].

Posttransplant lymphoproliferative disease (PTLD) and other malignancies can occur among lung transplant recipients. The incidence of PTLD after LT reportedly ranges from 1.8% to 9.4% [91]. PTLD comprises a heterogenous group of lymphoid proliferations, usually of the B-cell form, that are strongly associated with the Epstein–Barr virus (EBV). Patients for whom the results of pretransplantation serological studies are negative for EBV but who receive an organ from an EBV-positive donor and experience seroconversion are at a higher risk of PTLD. Clinically, PTLD usually occurs during the first year after transplantation; it involves the allograft and manifests itself as radiographic findings of solitary or multiple pulmonary nodules. Treatment includes reducing the level of immunosuppression, institution of antiviral therapy, and administering the anti-CD20 monoclonal antibody rituximab. In some cases, chemotherapy or surgery may be indicated.

Significant advances have been made in the field of LT since its inception more than 30 years ago, allowing this procedure to be a successful therapeutic option for patients with end-stage parenchymal or vascular lung disease. However, despite these improvements, numerous complications, many of which are managed by critical care professionals, can arise in this group of patients, and the unique aspects of their care are important.

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SECTION XV ■ METABOLISM/NUTRITION

DOMINIC J. NOMPLEGGI

CHAPTER 190 ■ NUTRITIONAL THERAPY IN THE CRITICALLY ILL PATIENT

DOMINIC J. NOMPLEGGI

The nutritional management of critically ill patients has changed dramatically over the past 10 years. Changes in the areas of nutritional assessment, guidelines for total energy provided, disease-specific feeding, and immune-enhancing enteral nutrition have been the most prominent. The rationale for nutrition support comes from the knowledge that critically ill patients are prone to develop malnutrition, which is known to be associated with serious complications such as sepsis and pneumonia, leading to a poor outcome and even death [1].

Although guidelines continue to be in evolution, there are sufficient data on clinically proven principles and methods of nutrition support to permit practical and useful recommendations for the specific problems and questions confronted by the intensivist.

The Society of Critical Medicine and the American Society for Parenteral and Enteral Nutrition convened an expert panel to review all available data in the literature to establish guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient [2]. These recommendations concluded that now after more then 30 years of investigation, nutrition *support* in critically ill patients, once regarded as adjunctive care designed to preserve lean body mass, maintain immune function, and avoid metabolic complications should now be considered nutrition *therapy* specifically aimed at attenuating the metabolic response to stress, prevent oxidative injury and improve the immune response [2]. Table 190.1 does not list all of the recommendations of the panel but summarizes all the recommendations supported by randomized trials.

WHAT IS MALNUTRITION AND HOW DO WE RECOGNIZE IT?

Malnutrition in ICU patients is common and can be present on admission or develop as a result of the metabolic response to injury. This response to injury can lead to changes in substrate metabolism, causing alterations in body composition and nutrient deficiencies that become clinically evident [3]. During starvation, the body uses fat and muscle protein as a source of energy in order to preserve visceral protein [4]. Mobilization of fat for fuel is an important adaptive response for survival because glucose stores, in the form of glycogen, provide only 1,200 kcal in the first 24 hours of starvation. The body attempts to use muscle protein rather than visceral protein because visceral protein is essential for vital functions of the body. Skeletal muscle mass decreases steadily, and its rate of loss exceeds that of weight loss [5]. Because these changes are difficult to assess, intensivists have had to resort to a variety of tools such as clinical, anthropometric, chemical, and immunological parameters that reflect altered body composition [6].

Nutritional Assessment

It is not known how long a critically ill patient can tolerate lack of nutrient intake without adverse consequences, but because critical depletion of lean tissue can occur after 14 days of starvation in severely catabolic patients, it is recommended that nutrition support be instituted in patients who are not expected to resume oral feeding for 7 to 10 days [7]. A recent study conducted by the European Society of Intensive Care Medicine (ESICM) surveyed intensivists from 35 countries using a 49-item questionnaire to determine how they cope with these issues and to assess the current practice of nutritional management in intensive care units (ICUs) [8].

In the ESICM study, 45% of the patients were fed within 24 hours and 47% between 24 and 48 hours of admission to the ICU [8]. The need for nutritional support is determined by the balance between endogenous energy reserves of the body and the severity of stress. The best clinical markers of stress are fever, leukocytosis, hypoalbuminemia, and a negative nitrogen balance.

The purpose of nutritional assessment is to identify the type and degree of malnutrition to devise a rational approach to treatment. Percentage weight loss in the patient's past 6 months, serum albumin level, and total lymphocyte count are readily available, commonly used measures to assess nutritional status. A 10% or 10-lb weight loss over the previous 12 months is an indicator of protein calorie malnutrition. This results from inadequate caloric intake. Hypoalbuminemic malnutrition or kwashiorkor is due to severe stress or profound malnutrition. Albumin is not a very sensitive indicator of malnutrition in ICU patients because its synthesis is influenced by numerous factors other than nutritional status such as protein losing states, hepatic function, and acute infection or inflammation [9]. Normal concentrations of albumin are unattainable in many critically ill patients because of large fluid shifts and inadequate synthesis to meet demands. Hypoalbuminemia should be viewed as a marker of injury and not as an indicator of impaired nutrition. Most critically ill patents have a combination of the two. The protein calorie malnutrition can be easily treated by supplying adequate caloric intake. The hypoalbuminemic malnutrition is most effectively treated by nutrition support and treatment of the stresses that led to this severe catabolic condition.

Traditionally, weight loss of 10 lb or 10% of usual weight is clinically important, weight loss of 20% to 30% suggests moderate protein calorie malnutrition, and greater than 30%, severe protein calorie malnutrition. Unfortunately, in many critically ill patients, total body weight is often an insensitive parameter because of progressive total body salt and water retention. Anthropometrics (i.e., measurement of triceps skinfold thickness and midarm muscle circumference) are reasonably accurate even in the presence of excess body water because edema accumulates to a lesser extent in the upper extremities

TABLE 190.1

SUMMARY OF EVIDENCE-BASED GUIDELINES FOR NUTRITION SUPPORT

- Enteral Nutrition (EN) is preferred over parenteral nutrition (PN) for critically ill patients who require nutrition support.
- Bowel sounds are not required for the initiation of enteral feeding.
- Immune modulating enteral formulations should be used for critically ill patients on mechanical ventilation but with caution in patients with severe sepsis.
- Patients with ARDS and severe acute lung injury require enteral feeding containing anti-inflammatory lipids (i.e., omega-3 fish oil, borage oil) and antioxidants.
- Antioxidant vitamins and trace minerals, specifically containing selenium, should be given to all critically ill patients receiving nutrition therapy
- EN regimens not containing glutamine should be supplemented with glutamine in burn, trauma and mixed critically ill patients.
- Protocols to promote moderately strict control of serum glucose levels (110–150 mg/dL) when providing nutrition support are recommended.

Adapted from McClave SA, Martindale RG, Vanek VW, et al: Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) *J Parent Enteral Nutr* 33:277–318, 2009.

[10]. However, they are difficult to perform in critically ill patients, time consuming, and not routinely performed. The general appearance of the patient, with emphasis on evidence of temporal, upper body, and upper extremity wasting of skeletal muscle mass, provides a quick, inexpensive, and clinically useful measure of nutritional status. For the reasons above, clinicians have found that body mass index may be a more practical way to assess nutritional status. As presented in Chapter 191, Driscoll suggests that a patient weight less than 85% of the ideal body weight (IBW) or BMI less than 18.5 indicates moderate malnutrition. Severe malnutrition would be considered likely if weight is less than 75% of IBW or BMI is less than 16 kg per m^2. Thus, a greater sense of urgency to intervene with nutrition support is present under these conditions and should be undertaken within several days of the acute injury.

Malnutrition is closely correlated with alterations in immune response as measured by skin test reactivity and total lymphocyte count. A total lymphocyte count less than 1,000 per mm^3 is indicative of altered immune function and is associated with decreased skin test reactivity. Loss of delayed cutaneous hypersensitivity to common antigens is a measure of impaired cellular immunity, which has consistently been found to be associated with malnutrition [9].

Subjective global assessment (SGA) is a method for evaluating nutritional status that uses clinical parameters like history, physical findings, and symptoms [11,12]. The SGA determines whether (a) nutritional assimilation has been restricted because of decreased food intake, maldigestion, or malabsorption, (b) any effects of malnutrition on organ function and body composition have occurred, and (c) the patient's disease process has influenced nutrient requirements [7].

As stated by the advisory committee convened by the National Institutes of Health, the American Society for Parenteral and Enteral Nutrition, and the American Society for Clinical Nutrition, "there is no 'gold standard' for determining nutritional status because (a) there is no universally accepted clinical definition of malnutrition, (b) all current assessment parameters are affected by illness and injury, (c) it is difficult to isolate the effects of malnutrition from the influence of the disease on clinical outcome, and (d) it is not clear which of the commonly used nutrition assessments techniques is the most reliable because of the paucity of comparative data" [7].

According to the ESICM questionnaire, the critical care community appears to most commonly assess nutritional status using the SGA and laboratory parameters [8]. Although there are no data to attest to the reliability of this approach in critically ill patients, serum albumin, stress level, weight loss in excess of 10% of ideal body weight, and SGA have been shown to be reasonable markers of nutritional status in noncritically ill hospitalized patients. Until future studies show otherwise, weight loss, serum albumin, and SGA are likely to be reliable parameters to follow in patients who are not volume overloaded. They are simple to measure, generally accepted, and commonly used.

HOW MUCH SHOULD YOU FEED?

Macronutrients

Body cell mass is the major determinant of the total caloric requirement. Energy needs can be estimated or measured directly using indirect calorimetry. Because estimated energy requirements have been shown to be adequate in most patients, direct measurement is usually reserved for patients in whom estimating energy needs are difficult or when patients do not appear to respond to therapy (e.g., worsening respiratory function, continued weight loss, or a decrease in prealbumin levels, a more sensitive marker of protein synthesis than albumin).

The general principle of macronutrient support is to provide enough energy to promote anabolic functions and avoid caloric overload. Caloric requirements of 25 to 30 kcal per kg should be based on the usual body weight and are adequate for most patients [2,9]. If patients are not responding to therapy as indicated by the parameters listed above, or if they are in a severe catabolic state as occurs in multiple trauma or burns patients, they may need 30 or even 40 kcal per kg.

Protein

The usual protein requirement has been estimated to be 1.2 to 1.5 g per kg per day for actual body weight. Nitrogen retention can be monitored and protein adjusted to support protein synthetic functions. Protein should be reduced when the blood urea nitrogen rises to 100 mg per dL or an elevated ammonia level is associated with clinical encephalopathy to limit the impact of the uremia and to avoid worsening encephalopathy associated with elevated ammonia levels [9].

Carbohydrates

Generally patients will need about 25 to 30 kcal per kg per day to meet there energy requirements. Approximately 20 kcal per kg per day of the actual body weight can be provided as carbohydrate. Levels of carbohydrate above 30 kcal per kg per day increase the risk of hyperglycemia. Hyperglycemia should be avoided because it is associated with abnormalities in granulocyte adhesion, chemotaxis, phagocytosis and intracellular killing, and poor clinical outcomes.

Hyperglycemia is a major contributing factor to postoperative infection. Blood sugars greater than 220 mg per dL on postoperative day 1 have been associated with a fivefold increased risk of serious infection [13]. A recent study in patients requiring total parenteral nutrition (TPN) to determine whether

the frequency of hyperglycemia and infectious complications can be reduced by an underfeeding strategy (1,000 kcal with 70 g per kg as protein) provision of 1.5 g per kg of protein in conjunction with 25 kcal per kg was not associated with more hyperglycemia or infections than deliberate underfeeding. However, a regimen of 25 kcal per kg in conjunction with 1.5 g per kg of protein did provide significant nutritional benefit in terms of nitrogen balance as compared with hypocaloric TPN [14]. This suggests that it is not a hypocaloric low carbohydrate formula that protects against infection but rather the avoidance of hyperglycemia. Alternatively, TPN can be adjusted and regular insulin given, as needed, to maintain a blood glucose level from 110 to 150 mg per dL [2].

Fat

Usually no more than 15% to 20% of total calories per day should be provided as fat. This will avoid infectious complications that may be due to dysfunction of the reticuloendothelial system, which has been associated with the administration of excess lipids [15]. Omega-6 polyunsaturated fatty acids should be provided in doses adequate to prevent essential fatty acid deficiency (at least 7% of total calories). Medium-chain triglycerides (MCT) can be administered with long-chain triglycerides (LCT). MCTs are more water soluble and require less lipase activity and bile salts for absorption. Patients with malabsorption, pancreatic insufficiency, and chronic liver disease can absorb them more easily. The ratio of MCT to LCT depends on the route of administration and product availability [9].

Electrolytes, Micronutrients, and Fluid

Potassium, magnesium, phosphate, and zinc should be provided in amounts necessary to maintain normal serum levels. The absolute requirements for vitamins, minerals, and trace elements have not yet been determined. Normal serum and blood levels of vitamins have been established but may vary with the laboratory in which the measurement is obtained [9]. In general, patients should receive 25 mL of fluid per kg actual dry body weight to avoid dehydration. Three milliliters of trace elements injection 5 (Multitrace-5®) and 10 mL of multiple vitamin infusion (Infuvite Adult®) will provide adequate vitamins, trace elements, and minerals and should be added to TPN daily. The required daily allowance (RDA) for all vitamins and minerals are usually provided in 1,000 to 1,500 mL of most enteral formulas. If the patient is receiving less than a liter of enteral feeding, vitamin supplementation may be necessary. Spot electrolyte measurements (aliquots of urine, ostomy, nasogastric, or fistulous output) may be very helpful in determining proper replacement. If the total daily volume of the lost fluid is measured, the daily loss of any electrolyte in that fluid can be estimated using the following equation: mmol per L × volume output per 24 hours (in liters) = mmol per 24 hours (e.g., 20 mL of urine contains 100 mmol per L, the daily urine output is 2 L; therefore, the 24 hour urine sodium output is 200 mmol).

WHICH ROUTE OF ADMINISTRATION?

Enteral Feeding

Enteral feeding has been shown in clinical studies to reduce infection and preserve gut integrity, barrier, and immune function. It is the preferred route of nutrient administration because it is more physiologic, safer, and less expensive than parenteral feeding. Current recommendations support initiation of enteral nutrition as soon as the patient is hemodynamically stable [2]. The only contraindication is a nonfunctioning gut. For example, intragastric feeding requires adequate gastric motility. Gastric residuals should be checked hourly and a volume greater than 200 mL necessitates modification of the infusion rate to minimize reflux and aspiration. Supplemental parenteral nutrition to meet caloric requirements or small bowel feeding to potentially decrease the risk of aspiration will be necessary until normal gastric function returns. Gastric atony and colonic ileus do not preclude enteral feeding but may require gastric decompression and small bowel feeding.

Initiation of enteral feeding does not require active bowel sounds or the passage of flatus or stool. Small bowel feedings can be given in the presence of mild or resolving pancreatitis and low output enterocutaneous fistulas (less than 500 mL per day) [2,8]. Recently, even patients with severe acute pancreatitis (acute physiology and chronic health evaluation [APACHE] II score 12 to 13) receiving enteral nutrition were found to have significantly fewer total complications and septic complications than patients receiving parenteral nutrition [16]. Worsening abdominal distention or diarrhea in excess of 1,000 mL per day requires a medical evaluation. If distention is present, enteral feedings should be discontinued. If no infectious cause for the diarrhea is found, antidiarrheals can be administered and feedings continued [9]. Nasogastric feeding is appropriate for most patients except those with a history of aspiration pneumonia associated with reflux. Those patients should be fed postpylorically or via a G-tube to minimize nasogastric tube-associated reflux of gastric contents and aspiration. Although there are some recent data suggesting it is just as safe to feed patients with severe pancreatitis intragastrically, the bulk of existing evidence favors feeding intrajejunally to minimize pancreatic stimulation [17].

Standard isotonic polymeric formulations can meet most patients' nutritional needs. The use of elemental formulas should be reserved for patients with severe small bowel absorptive dysfunction. The "American Gastroenterological Association Medical Position Statement: Guidelines for the use of enteral nutrition" has concluded that disease or organ-specific specialty formulations generally are more expensive and have a limited clinical role, and they will require more data to justify their practicality and effectiveness [18].

There are numerous issues that arise when providing enteral nutrition to critically ill patients. We provide guidelines to help the readers of this review overcome the problems that often arise when administering enteral tube feeding.

In general, most complications associated with the use of feeding tubes relate to placement, displacement, or malfunction of the tubes. It is important to remember that these tubes require frequent maintenance to avoid complications. The position of nasogastric or nasoenteric feeding tubes placed at the bedside should be confirmed endoscopically or radiographically before use because clinical assessment is unreliable. The use of promotility drugs has not been shown to be consistently beneficial and although they can increase the volume of feeding the overall impact is small [2,9]. Excessive force during insertion, which can result in malposition, should be avoided. Tubes need to be flushed regularly to avoid clogging with medications or tube feeding. Cycled tube feeding is recommended, if possible, to facilitate this. Little is known about compatibility of most medications with tube feeding and, therefore, medications should not be mixed with tube feedings since this can lead to precipitation of the medication with blockage of the tube and decreased absorption of the medication.

Placement of tubes across the gastroesophageal junction or pylorus can lead to incompetence of the sphincter, reflux, and aspiration. In patients at risk for or with a history of aspiration associated with reflux we recommend percutaneously

placed gastric or jejunal feeding tubes. Gastric tubes are preferred because the smaller caliber of the jejunal tubes makes them likely to clog with administration of anything except liquid medications. Percutaneously placed tubes that fall or are pulled out should be replaced cautiously. Unlike noncritically ill patients who usually have had their feeding tubes in place long term, critically ill patients are likely to have had their tube placed recently or may have impaired healing and, therefore, may not have a fully developed cutaneous fistula. For these reasons we recommend confirming placement with a contrast-enhanced radiograph before use when replacing these tubes at the bedside.

Elevating the head of the bed 30 degrees and checking for gastric residuals to avoid increases in the volume of the gastric contents, which can lead to hypersecretion and reflux of gastric contents, is also recommended.

Stress gastritis, also known as stress-related erosive syndrome (SRES), is a term used to describe gastrointestinal mucosal injury associated with serious systemic disease. Most patients at risk cannot have oral feedings. Histamine H_2 receptor antagonists (H2RAs) have been shown to protect against significant gastrointestinal hemorrhage. There are less data on the efficacy of proton pump inhibitors (PPIs). A reasonable suggestion has been to wait 6 to 12 hours between stopping parenteral H2RAs before starting to feed and initiating therapy with a PPI [19].

Parenteral Feeding

Parenteral nutrient administration is recommended when the gastrointestinal tract is nonfunctional or inaccessible or enteral feeding is insufficient. Although parenteral nutrient admixtures are not as nutritionally complete as enteral formulations, nutritional goals are achieved more often with the former than the latter. This is usually attributable to a variety of barriers. A recent study of four university-based ICUs at two hospitals found that physicians ordered a daily volume of enteral feeding that was 66% of the requirement, but because only 78% of the ordered volume was infused, patients received only 52% of target calories. Sixty-six percent of the time the reasons given for stopping the infusion were determined to be avoidable. Half the patients whose tube feedings were checked every 4 hours had their feedings held for residual volumes less than 200 mL, when the guideline for stopping the tube feeding was a residual of greater than 200 mL [20]. Protocols for delivery of enteral feeding can avoid this.

Parenteral nutrition is associated with an increased risk of infectious complications, especially line infection, and increased cost. Strict adherence to protocols emphasizing aseptic techniques and limiting central line interruption can decrease complications. Peripheral indwelling central catheters or central subclavian or internal jugular lines should be considered and implanted permanent lines should be avoided [9]. Management of infected temporary lines is easier and has fewer complications.

HOW DO YOU PREVENT COMPLICATIONS AND MAXIMIZE BENEFITS?

Anticipating potential complications leads to early recognition, minimizes the impact of the complications, and improves outcome. Adherence to general guidelines for energy requirements, mentioned above, should help avoid overfeeding. Overfeeding can lead to a number of problems, such as cholestatic liver disease, hyperglycemia, increased infections, and worsening hypercapnic respiratory failure. When there is doubt, expired gas analysis can be used to assess caloric requirements. A respiratory quotient (R/Q) greater than 1 generally indicates overfeeding. R/Q is the quotient of mL CO_2 produced per mL O_2 consumed. Increased CO_2 production will cause a rise in the R/Q from 0.80, a normal, average steady state. Reducing total calories (glucose and fat) may benefit patients with chronic lung disease fed parenterally who develop worsening hypercapnia. Assessment of nitrogen balance (the difference between nitrogen produced and nitrogen eliminated in urine and stool) every 5 to 7 days may be useful for adjusting the protein dose. Prerenal azotemia from excessive protein administration is an indication to decrease nitrogen intake. Patient outcome following acute renal failure (creatinine greater than twice normal) does not improve with the administration of specialized formulations.

Monitoring triglycerides and adjusting continuous fat infusion to keep triglycerides less than 500 mg per dL will avoid hypertriglyceridemia. Monitoring of prealbumin because of its short half-life (i.e., 2 days) can be used to assess response to feeding in the ICU setting. Monitoring of fluid and electrolytes is essential particularly in patients receiving TPN to avoid volume overload. Deficiencies in potassium or calcium can lead to cardiac arrhythmias. Hypophosphatemia can precipitate rhabdomyolysis, severe muscle weakness, and respiratory failure. Hypomagnesemia can cause muscle weakness and even seizures. Zinc deficiency can lead to impaired wound healing, diarrhea, and cutaneous anergy. Routine monitoring of vitamins and minerals in patients on short-term parenteral nutrition support is not useful because deficiencies are usually only associated with long-term therapy. Monitoring on a selected case basis when there are clinical signs or symptoms of a vitamin deficiency (e.g., hyperkeratosis [vitamin A], megaloblastic anemia [folate/vitamin B_{12}]) is more practical. Although liver enzymes should be monitored weekly to determine if biliary or liver disease has developed, specialized formulations are not indicated unless there are signs of encephalopathy [9].

WHAT IS THE IMPORTANCE OF PROVIDING SPECIAL KEY NUTRIENTS?

Effects of special nutrients on regulation of the processes of inflammation and repair and immune function have been the object of many recent studies. Although specialized nutrients added to parenteral or enteral formulas have been shown to modulate a variety of cellular responses, their precise clinical utility is still unresolved. For example, arginine is an amino acid that participates in a variety of metabolic processes, including synthesis of nitrous and nitric oxide, compounds known to protect the liver from damage in a murine model of endotoxin-induced hepatic necrosis [21], urea synthesis, lymphocyte proliferation, and wound healing. Other studies have shown that diets rich in fish oils increased survival in guinea pigs challenged with endotoxin [22,23].

The branched chain amino acids leucine, isoleucine, and valine are essential amino acids required for protein synthesis. Although improvement in nitrogen balance can be observed when these are given in combination with other essential amino acids in doses of 0.5 to 1.2 g per kg per day, their efficacy in improving patient outcomes remains to be defined [9,24].

The importance of glutamine to normal cellular function and its unique function in amino acid metabolism, in both health and disease, has recently been elucidated [25]. The skeletal muscle-free amino acid pool is 61% glutamine, and accelerated mobilization of glutamine occurs during catabolic states. In such states, glutamine depletion occurs despite

administration of standard parenteral amino acids, which do not contain glutamine because of their instability in aqueous solution. In rats, decline of the intracellular pool of glutamine in skeletal muscle has been shown to correlate with skeletal muscle protein degradation. The majority of glutamine released from skeletal muscle is taken up by intestinal cells. Rat studies have shown that glutamine-supplemented parenteral nutrition improves gut mucosal metabolism and nitrogen balance in sepsis and also increases villus height and mucosal thickness in starved rats, suggesting that mucosal barrier defense is improved [26,27]. However, in humans, a randomized trial of glutamine supplementation in parenteral nutrition detected no difference in infectious complications or median length of hospital stay between groups [28].

Addition of specialized key nutrients to enteral formulas to enhance immune function has been suggested for the reasons outlined earlier. A meta-analysis of 12 studies that used either of the two most common commercially available enteral feeding preparations enriched with the "immunonutrients" arginine and omega-3 fatty acids concluded that they had no effect on mortality [29]. However, significant reductions in infection rates, ventilator days, and hospital length of stay in patients fed these formulas are sufficient to justify their use. These benefits were most pronounced in surgical patients, although they were present in all groups of patients [29]. Although the relative efficacy of any single immune-enhancing component versus its combination with another is impossible to state on the basis of the presently available evidence [30], commercially available formulas fortified with "immunonutrients" are clearly beneficial and we recommend their use [2].

Although the administration of growth hormone can attenuate the severe catabolic state induced by the metabolic response to injury, surgery, and sepsis, two randomized placebo-controlled clinical trials found that in-hospital mortality, length of stay in the ICU, and duration of mechanical ventilation were greater in patients receiving growth hormone [31].

In summary, nutrition support should be considered essential to the treatment of any critical illness. We have provided some useful guidelines for the nutritional assessment, estimation of energy requirement, route of nutrient delivery, estimations of the effectiveness of nutrition provided in critically ill patients, and also suggested some practical points to simplify delivery and avoid associated complications related to parenteral and enteral feeding.

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CHAPTER 191 ■ PARENTERAL AND ENTERAL NUTRITION IN THE INTENSIVE CARE UNIT

DAVID F. DRISCOLL AND BRUCE R. BISTRIAN

Nutritional and metabolic support during acute illness is an integral part of the clinical care of critically ill patients. The significance of such interventions is predicated on three main factors: (a) degree of metabolic stress; (b) dysfunction of major organ systems; and/or (c) presence of protein-calorie malnutrition (PCM). In the first case, metabolic stress can arise from a variety of sources including, for example, severe injuries sustained by major trauma such as closed head injury, multiple long-bone fractures, third-degree burns of greater than 25% body surface area, and severe sepsis and stress of lesser intensity such as thoracoabdominal surgery, pulmonary infection, systemic infection, or any source of active systemic inflammation. Often, more than one form of metabolic stress may be present that can accentuate and/or dysregulate the injury response. Concerning the second factor, metabolically stressed patients may develop acute failure of vital organs during the critical care period or have underlying chronic end-organ dysfunction. Acute or chronic disease, particularly of the cardiopulmonary, renal, or hepatic system, often further complicates the clinical course and requires modification of nutritional support during critical illness, especially in the elderly [1]. Finally, the presence of preexisting or the likely early development of PCM is key to identifying those patients who will derive the greatest clinical benefits from nutritional and metabolic support therapy.

Approximately 35 years ago, the prevalence of PCM in hospitalized general medical and surgical patients was reported to be as high as 50% of all adult admissions to a large teaching hospital [2,3]. More recent reports continue to document high rates of malnutrition in hospitalized patients [4–9]. When moderate to severe PCM accompanies severe metabolic stress, an increase in nutrition-related complications can be expected to occur, including wound dehiscence, nosocomial infections, and severe fluid, electrolyte, and acid–base disturbances. During stress, substantial catabolism of both endogenous and exogenous protein and energy occurs coincident with the injury response. In support of the metabolic response to injury, the breakdown of body protein, principally from muscle and connective tissue stores, supports amino acid and energy needs to mount various beneficial components of the systemic inflammatory response by the release of amino acids for accelerated synthesis of such proteins as leukocytes, hepatic acute phase and cellular proteins, and wound tissue, and gluconeogenesis for the optimization of energy requirements for such tissues as cardiac, leukocytes, and fibroblasts. An assessment of the degree of this response can be estimated by application of the catabolic index [10]. However, if protein calorie malnutrition complicates injury or infection, the systemic inflammatory response is less intense than that found in normally nourished individuals with a similar degree of injury. Consequently, the degree and duration of the metabolic response, with respect to nitrogen breakdown, is greatly diminished. In terms of the degree of catabolism, for example, a malnourished elderly patient with significant catabolic injury could manifest nitrogen losses that may be as a much as 50% less than normally nourished younger counterparts with the same injury [1]. Although this might imply a less severe catabolic response sparing lean tissue, the pathologic consequences are more severe as a result of the muting of the beneficial aspects of the systemic inflammatory response, and these adverse effects tend to occur sooner. Moreover, the time course to intervene with nutritional and metabolic support to limit the likelihood of nutrition-related complications is also shortened by as a much as 50% (i.e., 5 to 7 days) in the moderate to severely malnourished versus normally nourished individuals (i.e., 7 to 10 days) with the same metabolic stress. Ultimately, the consequences of ongoing depletion of the metabolically active body cell mass in the malnourished reduce the ability to recover from acute illness, can be associated with severe deficiencies in minerals that are typically found in muscle (potassium, magnesium, and phosphorus), and often lead to severe impairments in immunocompetence, wound healing, and organ repair.

Once the decision to provide nutrition support is made, parenteral or enteral nutritional therapies are available options. In every case, if the gastrointestinal tract is functional and the patient is hemodynamically stable, enteral nutrition (EN) should be instituted. However, if significant malnutrition also exists and a prolonged recovery is anticipated, it should be recognized that the time frame to achieve eucaloric intakes for EN often takes much longer due to associated gastrointestinal intolerance, compared with parenteral nutrition (PN). As central venous access is generally necessary during critical illness, EN support can often be supplemented with PN [11] so as to avoid the prolongation of caloric deficits during acute illness, which are particularly of concern in initially malnourished patients or the most critically ill with closed head injury, multiple trauma, major burns, and severe sepsis. In such patients it appears that early feeding within the first 72 hours, whether by enteral, parenteral, or the combination, has the greatest impact on outcome in terms of mortality. Although mild decrements in energy balance in the critical care setting may well be tolerated and in certain circumstances appropriate, at least 1 g of protein per kg and 15 kcal per kg advancing to 1.5 g protein per kg and 20 to 25 kcal per kg as soon as possible should be the goal to avoid adverse, nutrition-related outcomes. Moreover, intensive metabolic support (i.e., the provision of electrolytes and acid–base therapy) can also be accomplished efficiently through the PN admixture. The amount of parenteral nutrients can be gradually reduced as the patient is transitioned to EN coincident with remission of the stress response and return of full gastrointestinal tolerance to tube feeding. Thus, in the intensive care unit (ICU), nutrition support is often provided to patients using both enteral and parenteral means, especially during the acute care period. The purpose of supplying both EN and PN where appropriate should not be motivated by attempts to meet protein and energy needs as soon as possible, but rather as a means of providing trophic stimulation to enterocytes and hopefully a quicker transition to full enteral feedings, while PN is used to treat severe metabolic disorders such as hypokalemia, hypophosphatemia, and metabolic alkalosis, that can only be safely and effectively addressed by the

intravenous route of administration. The greatest challenge facing the critical care clinician is to appropriately identify those patients who are in greatest need of nutrition support therapy and to provide it in a manner that is both effective and does not produce iatrogenic complications.

CLINICAL CONSEQUENCES OF DELAYING NUTRITION SUPPORT

Although at times it is difficult to pinpoint the cause and effect of nutrition-related complications during critical illness, it should be intuitively obvious that withholding nutrition will ultimately lead to death from starvation. This message was poignantly illustrated in the deaths of Maze prisoners in Belfast, Ireland, as detailed in a report from Leiter and Marliss [12] in 1982. Ten Irish Republican Army prisoners went on a hunger strike that led to their deaths over a period of 45 to 73 days of fasting. All were young lean males and the critical weight loss that resulted in death was approximately 35% calculated from the first day of the fast. It is also generally acknowledged that patients who approach 35% to 40% losses from their ideal or usual body weight through inadequate nutritional intake are at greatest risk of malnutrition-related death. Presumably, at these extreme levels of body mass depletion, both the size and function of vital organs of the viscera are considerably diminished. At some critical point, presumed to be when fat stores become limited, protein catabolism now coming from both skeletal and visceral organs accelerates. If one discontinues providing life-sustaining needs for energy, the loss of a critical mass of body protein is ultimately reached and death from organ failure is imminent.

The effects on the vital organs can be catastrophic, since oxygen consumption of the visceral organs is much higher than that of resting skeletal muscle. The imbalance between loss of skeletal muscle and visceral organ mass initially favoring visceral organs has also been suggested to explain the higher energy expenditures per body weight seen in severely depleted hospitalized patients (average of approximately 70% of ideal body weight) as a result of an approximate 10-fold difference in resting oxygen consumption between skeletal muscle compared to visceral tissues such as the liver [13]. During starvation (with adequate water intake), and in the absence of metabolic stress, a normally nourished, thin individual can survive for periods of approximately 6 to 10 weeks. In terms of total body nitrogen, it is estimated that the loss of 350 to 500 g of nitrogen is potentially lethal. In terms of body mass index (BMI), which is weight in kg per height in meters squared, it is generally considered that a BMI less than 13 kg per m^2 in males and less than 11 kg per m^2 in females is incompatible with life [14]. However, the rapidity of weight loss is also a factor, since lesser degrees of semistarvation (i.e., smaller energy deficits) are better tolerated. Table 191.1 depicts the relationship of BMI with nutritional status.

By way of comparison, the metabolically stressed patient experiences greater catabolism coincident with acute illness and can lose as much as 30 g of nitrogen per day, representing about 1 kg of lean tissue from the breakdown of lean body mass. Generally, the majority of these losses can be measured in a 24-hour urine collection as urea nitrogen and used for nitrogen balance estimation. Nitrogen balance studies assess the difference between dietary protein (nitrogen) intake and nitrogen excretion. Healthy individuals consuming an adequate diet in terms of essential nutrients including protein (0.8 g protein per kg per day) and sufficient energy to provide energy balance will be in zero nitrogen balance. That is the nitrogen in is equaled by the nitrogen out in urine (mostly) and feces, reflecting no net change in lean body mass. Net nitrogen losses in patients receiving parenteral or enteral feeding can vary from 0 to 30 g per day, depending on the extent of the injury response and the level of feeding. With the systemic inflammatory response, the utilization of protein to maintain lean body mass is impaired, making the daily requirement increase to about 1.5 g protein per kg per day. Similarly, energy requirements increase, which are offset to some degree by the reduction in physical activity characteristic of the hospitalized patient. With the development of renal dysfunction, the proportionate amounts of nitrogen found in the urine become substantially less, with a concomitant rise in blood urea nitrogen (BUN). In general, in a 70-kg male every 5 mg% change in BUN represents 2 g of nitrogen catabolized and not excreted, and 1.5 g of nitrogen for a 60-kg female, based on average total body water of 60% and 50% for males and females, respectively. Protein intakes must be adjusted to limit the rise in BUN, but nutrition efficacy should not be sacrificed to renal function beyond a reduction to the 1 g protein per kg for other than very brief periods. Renal replacement therapy such as dialysis or hemofiltration should be considered in those circumstances. Once the BUN becomes stable, even if elevated by impaired renal function, a 24-hour urine urea nitrogen excretion represents the amount catabolized over that period. The catabolic index (CI) (CI = 24-hour urine urea nitrogen − [0.5 × dietary nitrogen + 3]), adjusts for the effects of dietary intake and obligatory nitrogen loss on urinary urea nitrogen excretion. The catabolic index is the difference between measured and predicted urine urea nitrogen excretion. For example, the major catabolic stresses that produce the highest nitrogen losses and catabolic indices include burns, head injury, severe sepsis, and multiple trauma. The clinical application of nitrogen balance and CI assessments are illustrated in Table 191.2.

There are potential clinical scenarios that may affect the accuracy of nitrogen balance studies. This is especially true in patients with renal dysfunction that may reduce nitrogen output and could erroneously suggest an improvement in nitrogen balance. A correction of the nitrogen balance study can be applied to account for the nitrogen losses that do not appear in the urine, but result in an increase in the BUN concentration. Assuming nitrogen intake remains constant, two important pieces of data are required to correct for the nitrogen losses not appearing in the urine and include the patient's BUN and body weight at the beginning and end of the 24-hour collection period. These are important because most of the urea is distributed in total body water. A clinical example that applies to this method of correction appears in Table 191.3.

In terms of lean body mass, each gram of nitrogen lost represents approximately 30 g of (hydrated) lean tissue (hydration ratio: approximately 4 or 5 to 1). For patients with daily

TABLE 191.1

BODY MASS INDEX AND NUTRITIONAL STATUS

Body mass index	= weight in kg ÷ (height in m)^2
Assumptions:	weight: 75 kg; height: 1.84 m
BMI	= 75/(1.84)^2
	= 22.2
Body mass index	Nutritional status
≥ 30	Obese
≥ 25 − < 30	Overweight
20 − < 25	Normal
< 18.5	Moderate malnutrition
< 16	Severe malnutrition
< 13	Lethal in males
< 11	Lethal in females

TABLE 191.2

CLINICAL APPLICATION OF THE NITROGEN BALANCE AND CATABOLIC INDEX ASSESSMENTS[a]

Nitrogen balance	$= \frac{\text{protein intake (g)}}{6.25} - (24\text{ h UUN} + 4)$ $= \frac{105\text{ g}}{6.25} - (20 + 4)$ $= -7.2\text{ g}$
Catabolic index	= UUN (g) − ($^1/_2$ × dietary nitrogen + 3) = 20 g − (0.5 × 16.8 g + 3) = 8.6 (severe stress)
< 0 no significant stress	
0–5 significant stress	
> 5 severe stress	

[a]Assumptions: 70 kg male; 105 g protein intake; 20 g UUN over 24 hours.
UUN, urine urea nitrogen.

nitrogen losses of 30 g, which represents the highest catabolic nitrogen loss in the absence of dietary protein intake, approximately 1 kg of lean tissue would be lost each day. Such losses cannot be sustained for protracted periods, and under these circumstances, nutrition support is clearly indicated within the first 24 to 36 hours even in the previously well-nourished patient to address this extraordinary rate of loss. Using cumulative nitrogen deficits of 350 to 500 g, a sustained loss of this magnitude could theoretically result in death in approximately 2 to 3 weeks, although catabolic rates usually diminish in the later weeks of injury. For the severely malnourished patient of 75% ideal body weight, one can estimate the critical survival period to be in the range of 1.5 to 2 weeks under the same circumstances. Finally, a cumulative caloric deficit of 10,000 kcal or more during acute illness has been associated with significant morbidity and mortality in the surgical ICU [15]. However, it is likely that the associated protein deficit played the larger role, since normal individuals have more than 150,000 stored calories as fat, which always makes up the greater proportion of the caloric deficit. A study in the medical ICU has shown that intakes of less than 25% of requirements were associated with a higher rate of bloodstream infections [16].

Of course, projections of survival or complications are estimates and may be highly variable depending on other factors (i.e., nutritional status, metabolic stress[es], end-organ function, and so forth). Moreover, in the clinical setting, such high outputs of nitrogen over long periods will not likely be sustained, as medical and surgical therapies will usually be successful in reducing the stress response. Furthermore, both the rate of reduction in lean body mass and the intensity of the systemic inflammatory response diminish as PCM develops. Such patients will invariably receive calories (dextrose) and electrolytes from various parenteral infusions, so that some form of supplementation is given, which also slows the loss of lean tissue. Consequently, the outcome of death from the total lack of nutrition support is rare. However, nutrition-related complications, such as impaired wound healing and immunocompetence leading to nosocomial infection, are the common proximate causes of increased morbidity and mortality under such circumstances.

IDENTIFYING PATIENTS IN NEED OF NUTRITION SUPPORT

In the ICU setting, it is often difficult to identify those patients who are at greatest risk of developing nutrition-related

TABLE 191.3

NITROGEN BALANCE CORRECTION IN RENAL DYSFUNCTION[a]

Prenitrogen balance data	
BUN = 31 mg/dL; weight = 70 kg; 105 g protein intake	
Prestudy	
Total body water @70 kg	= 42 L
Total BUN @31 mg/dL	= 42 L × 310 mg/L (or 310 mg/L) = **13,020 mg or 13 g**
Postnitrogen balance data	
BUN = 51 mg/dL; weight = 74 kg; 105 g protein intake; 24 h UUN = 20 g	
Poststudy	
Total body water @74 kg	= 42 L + 4 L = 46 L
Total BUN @51 mg/dL (or 510 mg/L)	= 46 L × 510 mg/L = **23,460 mg or 23.5 g**
Nitrogen balance	$= \frac{\text{protein intake (g)}}{6.25} - (24\text{ h UUN} + 4)$ $= \frac{105\text{ g}}{6.25} - (20 + 4)$ $= -7.2\text{ g}$
Corrected N-balance	= 13.02 g − 23.5 g urea nitrogen (blood) = −10.5 g not excreted in urine = −10.5 g (BUN) + (−7.2 g UUN) = **−17.7 g**

[a]Assumptions: Total body water = 60% (for males).
BUN, blood urea nitrogen; UUN, urine urea nitrogen.

complications due to preexisting malnutrition. Such patients are often volume overloaded due to massive administration of parenteral fluids from multiple drug therapies and often acute volume resuscitation, as well as maintenance intravenous therapy to support intravascular volume. This fluid retention and weight gain is often compounded by the hormonal consequences of the systemic inflammatory response such as enhanced insulin, aldosterone, and antidiuretic hormone secretion, which favor salt and water retention. Consequently, the weight of the patient is artificially high, and major efforts of the ICU team are often directed at reducing volume intake in order to mobilize third-space fluids. A weight history may be difficult to obtain or overlooked entirely because of more acute clinical issues. Moreover, an accurate patient weight is also important to optimize drug therapy. Under these circumstances, a moderately to severely malnourished patient may escape detection by the primary care team, and only be recognized as malnourished after fluid homeostasis is achieved, or worse, a potentially preventable nutrition-related complication, such as wound breakdown, occurs. Clearly, at this point, the opportunity to minimize such complications from expert nutrition support has passed, and the course toward rehabilitation may be long and costly.

To avoid this scenario, a more substantial effort must be undertaken to identify the patients at greatest risk. Nutrition screening programs on admission, especially by dieticians, can greatly assist in identifying these patients, but many patients, especially acute admissions for emergent care, may escape this surveillance process. In these cases, the premorbid weight is very important and should be obtained if at all possible. It will at least provide a baseline prior to the numerous medical and surgical maneuvers that may take place over the ensuing 24 to 48 hours that could dramatically change the patient's weight in the critical care setting.

If the admission weight is not obtained, then the clinician may need to estimate the patient's body weight from available hospital data. Estimations may be made based on the most recent weight recorded, and then backtracked through the medical chart using the intake and output records to reconstruct the original weight history. For critically ill patients, such records are usually reliable, and a reasonable estimate may be made. This estimate may be confirmed by subsequent discussions with the patient or family. When confirmed, the body weight can then be compared to standard measures for population-based body weight for height tables such as the ideal body weight or the BMI. A patient weight less than 85% of the ideal body weight (IBW) or BMI less than 18.5 indicates moderate malnutrition. Severe malnutrition would be considered likely if weight is less than 75% of IBW or BMI is less than 16 kg per m^2. Thus, a greater sense of urgency to intervene with nutrition support is present under these conditions and should be undertaken within several days of the acute injury. If the patient is deemed well nourished, then intervention may be delayed unless the systemic inflammatory response is severe (i.e., major third-degree burns, closed head injury with a Glasgow Coma Score less than 8, multiple trauma with very high acute physiology and chronic health evaluation [APACHE] or injury severity scores, severe pancreatitis with a positive CT scan and more than three Ranson criteria, and so forth). Then, because the systemic inflammatory response is likely to endure beyond 1 week, very early nutritional support is indicated. The serum albumin level, which reflects the presence of a recent systemic inflammatory response, is not often helpful in this setting because the invariable systemic inflammatory response and common disturbances in volume status make hypoalbuminemia universal. However, severe hypoalbuminemia (less than 2.4 g per dL) usually reflecting a greater degree and/or longer duration of systemic inflammation identifies a population at much greater nutritional risk. Finally, if the weight-based data are not reliable, a formal nutrition support consult or indirect calorimetry may be indicated.

NUTRITIONAL REQUIREMENTS

Protein

The amount and type of protein administered to the critically ill depend on the clinical circumstances of each patient. Nevertheless, there is an upper limit to the quantity of protein that can be given based on net protein utilization during metabolic stress. In general, providing protein in amounts above 1.75 g per kg per day exceeds the capacity of the body to use the administered protein to increase synthesis [17,18]. Amounts above this level of intake are essentially completely converted to urea and serve no nutritional purpose. At intakes ranging between 0.6 to 1.75 g per kg per day, each increment of intake increases net protein synthesis at a cost of increasing the proportion going to ureagenesis. In patients with nitrogen accumulation disorders (of either renal or hepatic origin), a compromise must often be made between greatest rates of net protein synthesis and lowest rates of urea or ammoniagenesis. For example, as the BUN increases, especially above 100 mg%, the risk of uremic complications increases, including bleeding, or, increasing the production of ammonia in encephalopathic patients. Generally, the optimal protein intake in critically ill patients is given at twice the recommended daily amount (approximately 0.8 g per kg per day) of normal adults, at approximately 1.5 g per kg per day. With renal impairment, at least 1 g per kg should be provided and greater amounts given if tolerated or dialysis is initiated. In patients with liver failure at least 1 g per kg of standard protein should be provided and up to 1.5 g per kg if tolerated. This is done recognizing the overall impairments in protein utilization that accompanies metabolic stress, as well as the heightened needs during catabolism.

The type of protein administered varies with the patient's condition and the route of administration. For PN support, standard protein mixtures are given in their monomeric form as individual crystalline amino acids and levorotatory isomers, which comprise the essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) and the nonessential amino acids (alanine, aminoacetic acid, arginine, cysteine, proline, serine, and tyrosine). In standard amino acid formulations, the branched-chain amino acids (leucine, isoleucine, and valine) comprise approximately 18% to 25% of the amino acid profile. Collectively, they are available in commercial intravenous solutions in concentrations ranging from 3% to 15%. On average, for every 6.25 g of the amino acids in the mixture, 1 g of nitrogen is available, although this number is lower with a number of the specialized amino acid formulas. The caloric value of protein is 4.1 kcal per g, and such calories should be counted in critically ill patients when tracking energy intakes.

Specialized amino acid mixtures have evolved that include selected profiles. For example, renal formulations have been devised that principally provide the essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine), while hepatic formulations have eliminated or reduced aromatic amino acids (phenylalanine, tryptophan, and tyrosine) and the sulphur-containing amino acid methionine and increased the proportion of branched-chain amino acids (BCAAs) (isoleucine, leucine, and valine). However, the routine use of these expensive formulations in these conditions over conventional or standard amino acid mixtures has not been convincingly demonstrated, and in certain cases when used to meet full protein needs, may be harmful [19]. For patients with nitrogen accumulation

disorders, the use of branched-chain enriched amino acid formulas in the range of 45% to 50% of the total amino acid profile have been shown to improve protein utilization when total amino acid intakes are given in the 40- to 70-g range and may reduce the risk of encephalopathy when compared to a standard formula. Finally, other attempts at modifying the profiles of amino acid mixtures, such as the extemporaneous preparation by the hospital pharmacy of sterile glutamine in total parenteral nutrition (TPN), have shown some benefits in selected settings but they require a considerable level of parenteral compounding expertise. In addition, in order to safely provide this compounded sterile preparation, ongoing quality assurance measures as outlined by the *United States Pharmacopeia* must be performed and therefore such practices are subject to Federal Drug Administration oversight [20]. A glutamine-containing dipeptide formulation, which is commercially available in Europe, has been the subject of some positive trials, but its ultimate place in the care of the critically ill is not yet established.

For EN support, protein is typically provided in either an oligomeric form as protein hydrolysates containing various peptides ranging from di- and tripeptides to polymers of eight or more, or as whole protein usually provided as casein or in its polymeric form as, for example, casein hydrolysates. Less commonly, they can even be provided as the individual amino acids. Most formulations contain a fixed amount of protein in the range of 30 to 40 g per L and thus for fluid-restricted patients in the ICU cannot meet the protein needs of most patients. Alternatively, more concentrated enteral formulae exist that may be used, or the clinician may opt to add protein modules to conventional products to increase protein density. However, in either case, both approaches result in higher osmolarities that may affect gastrointestinal tolerance.

Carbohydrate

The amount and type of energy provided to improve the utilization of the prescribed protein intake also varies with the individual patient. As well, there are physiologic limits to the amounts given, beyond which significant complications are more likely. For most patients, providing 25 kcal per kg per day is sufficient to support the protein synthetic response to metabolic stress. This is the total energy expenditure of most critically ill, postoperative patients. Amounts above 30 kcal per kg per day exceed the energy expenditure of most hospitalized patients except those with severe burns, closed head injury, and multiple trauma where measured caloric expenditures are usually 30 to 40 kcal per kg. However, providing nutritional support in amounts greater than 30 kcal per kg leads to higher rates of hyperglycemia in both types of patients; in the postoperative setting, due to overfeeding, and in the trauma unit, due to the severity of systemic inflammatory response. Although better glycemic control through the use of insulin would be one way to reduce the infectious risk in the latter instance, it is interesting to note that in several trials of immune-enhancing diets that improved outcomes and reduced infection rates have been seen at energy intakes at 30 kcal per kg or less, in diets that are likely to have been hypocaloric [21]. For carbohydrates, the physiologic limits are linked to the normal endogenous hepatic production rates for glucose, which approximate 2 mg per kg per minute or about 200 g per day for a 70-kg healthy adult [22]. This is the amount of glucose needed by the body to meet the obligate needs of tissues dependent on glucose (i.e., brain, renal medulla, red blood cells, and so forth), and it is derived from body stores of glycogen (glycogenolysis) or made from noncarbohydrate sources such as from protein breakdown to gluconeogenic amino acid precursors (gluconeogenesis). Glycogen stores are limited and therefore can be rapidly depleted during acute metabolic stress (i.e., within 24 hours) [23]. Thus, the major source of glucose in the hypocaloric state following stress comes from gluconeogenesis, and higher amounts than usual are produced to support the metabolic response to injury, accelerated by the hormonal milieu produced by the increased secretion of catecholamines, glucagon, cortisol, and growth hormone [24]. The judicious provision of nutrition support is designed to attenuate the extent of protein breakdown without exacerbating significant changes in nutritional and metabolic homeostasis. Similar to the case with protein, as carbohydrate intake increases net oxidation occurs, but with an increasing proportion going to nonoxidative pathways (glycogen synthesis and particularly de novo lipogenesis). However, glycogen synthesis is limited by available storage capacity of about 500 g in normal adults and perhaps 1,000 g in a critically ill patient receiving TPN, with its resultant very high insulin levels. There is effectively no limit for fat storage. The optimal balance is at intakes at about 400 g per day, with maximal glucose oxidized of 700 g per day. Thus, in a 70-kg adult, glucose to amino acid of 2:1 TPN formula providing glucose at 400 g per day and 1.5 g of protein per kg per day represents about 25 kcal per kg per day.

For PN, glucose is the only reasonable carbohydrate fuel or energy source that is widely available for intravenous administration. Generally, it is provided as a monohydrate and its caloric equivalent is therefore 3.4 kcal per g rather than 4 kcal per g for its anhydrous form. It is commercially available in a variety of concentrations ranging from 2.5% to 70% in sterile water for injection. Glucose is the primary energy source of any PN admixture prescribed for central venous alimentation and typically is given in final admixture concentrations from 10% to 25%. Higher concentrations can be given, but are associated with an increase in the number of dextrose-associated complications if the amounts given are too large.

For EN, carbohydrates may be given in a number of chemical forms. For example, they can be given as the monosaccharide, glucose, frequently found in monomeric or elemental formulas. Alternatively, in less refined formulas, carbohydrates may be provided as oligosaccharides, such as hydrolyzed cornstarch, or more complex polysaccharides, such as corn syrup, are frequently used. The selection of a particular enteral formula is largely based on a number of clinical factors such as gastrointestinal function, fluid status, and end-organ function.

Fat

Lipids serve as an alternative energy source that is used to substitute for a portion of the carbohydrate calories. PN support prescribed in this fashion, it is referred to as a total nutrient admixture, all-in-one or 3-in-1 mixed-fuel system [25]. As with protein and carbohydrates, the amount and type of lipids used will vary depending on the clinical condition of the patient. For the most part, long-chain triglycerides (LCTs) derived from vegetable oils have been the principal source of lipid calories used in the clinical setting. Specifically, soybean oil, which is rich in polyunsaturated omega-6 fatty acids, has been extensively used, especially for intravenous nutrition. It is a major source of the essential fatty acids, linoleic, and alpha linolenic acids. However, ill-considered prescribing habits, where either excessive quantities or infusion rates have been used, have led to clinically significant adverse effects such as immune dysfunction and pulmonary gas diffusion abnormalities in critically ill patients. The excessive administration of intravenous lipid emulsions (IVLE) can accumulate in the liver and impair Kupffer cell function, thus interfering with a major component of the reticuloendothelial system [26,27]. In addition, lipid injectable emulsions are composed of various oils that serve as prostaglandin precursors that are immunosuppressive,

especially those of the n6 series such as PGE_2, which suppresses lymphocyte proliferation and natural killer cell activity [28], and can reverse hypoxic vasoconstriction in patients with adult respiratory distress syndrome [29]. In contrast, the oxidation and subsequent plasma clearance of lipids is significantly improved when IVLEs are given over 24 hours versus briefer intervals [30]. Impaired plasma clearance of lipids can result in fat overload syndrome and is a particularly significant clinical issue in children [31–42]. Fat overload syndrome can result from the administration of a stable fat emulsion over brief intervals [29,30,43–47] or from more modest doses of lipid that might be physicochemically unstable [48]. In fact, a review of the literature regarding *stable* fat emulsions has concluded that virtually all of the adverse effects associated with LCTs have occurred when the infusion rate exceeds 0.11 g per kg per hour [49]. For a 70-kg adult this limit would be approximately 13 hours for 500 mL of 20%, which makes 3-in-1 admixture infusions safer and easier to administer as a continuous infusion over 24 hours rather than as a separate "IV piggyback" over a brief period, which would require an infusion rate almost twice as fast. In addition, piggyback infusion of lipids is not recommended beyond 12 hours [50].

Recent reports regarding the clinical significance of unstable fat emulsions have emerged. On December 1, 2007, the United States Pharmacopeia (USP), which is recognized by the Food and Drug Administration (FDA) as the official compendium for drug standards, was the first pharmacopeia worldwide to establish globule size limits for intravenous lipid emulsions [51]. This is notable because intravenous lipid emulsions had been used clinically in the United States for more than 30 years (and Europe for more than 45 years), when most drugs have official USP specifications within 5 years of FDA approval [52]. The USP limits specified two size limits: (i) mean droplet size (MDS < 0.5 µm) and (ii) large diameter tail, expressed as the percent of fat globules > 5 µm ($PFAT_5 < 0.05\%$). The primary motivation for these limits was to avoid the development of microvascular pulmonary embolism from an excessive population of large-diameter fat globules indicating instability of the emulsion.

Around the time the USP announced its intentions to adopt these limits in 2004 [53], a major lipid emulsion product also changed its conventional packaging from glass to plastic containers. With this change in packaging, the lipid emulsion product now failed the large-diameter globule limits of the USP [54]. Lipid emulsions failing USP limits were also shown to produce less stable emulsions when packaged in syringes for neonates [55], when mixed in TPN admixtures [56] and when used in a multichamber bag premixed for TPN therapy [57]. Moreover, lipid emulsions not meeting pharmacopeial limits were also shown to be associated with significant hypertriglyceridemia in premature neonates when compared to lipid emulsions meeting USP limits [58], although this has not been confirmed in a randomized clinical trial. Finally, in animal studies lipid emulsions failing USP limits were shown to be hepatotoxic [59]. A recent study intended to explore the extent of physiologic damage from the infusion of unstable lipid emulsions produced evidence of hepatic accumulation of fat associated with oxidative stress, liver injury and a low-level systemic inflammatory response [60].

Triglyceride clearance is maximal at serum triglyceride levels of up to about 400 mg per dL, and patients who initially have serum triglycerides at this level will tolerate even lesser amounts of fat without adverse consequences. In patients who have normal serum triglyceride levels at initiation of TPN, serum triglyceride levels are usually not monitored. For those with levels greater than 200 mg per dL it is reasonable to check the triglyceride again after a stable regimen has been attained with lipids below 0.11 g per kg per hour. Stable levels below 400 mg per dL are acceptable while receiving lipid emulsions.

For PN therapy, soybean oil emulsions continue to dominate the United States market. However, there are a number of different lipid compositions presently available in Europe and under investigation in the United States [61]. They include various mixtures of soybean oil with medium-chain triglycerides (MCTs), olive oil, and fish oil. In nearly every case, soybean oil is included in sufficient proportions to provide adequate amounts of the essential fatty acids [62].

For EN therapy, a number of the lipid types available for parenteral use in Europe are widely available in the United States for enteral administration in complete nutritional diets. Typically, they contain 30% to 40% of the total calories as fat and often contain blends of corn and soy oil. However, in the more specialized enteral formulas, MCTs, fish oil, and even structured lipids are available. Moreover, in some of these products the fat content is either severely restricted (i.e., 3% to 10% of total calories for the fat-intolerant patient) or may be as high as 55% for the patient with pulmonary compromise.

Volume

The maintenance of fluid homeostasis is an important goal in critical care. At times, many patients in the ICU become severely volume-overloaded as a consequence of parenteral fluid administration and the fluid-retentive state characteristic of critical illness [63–65]. For this reason, when assessing fluid status, it is important to bear in mind the usual contribution of water to body weight or total body water (TBW) of the patient under normal, unstressed conditions. In normal adults, TBW comprises approximately 50% to 60% of body weight. As lean body mass is hydrated in a ratio of approximately 4 parts water to 1 part protein, lean tissue is a significant component of TBW. In the clinical setting, acute changes in weight over short intervals primarily reflect net changes in TBW which almost never reflect lean tissue gains in the hospital setting. For example, a 10% increase in weight over 24 to 48 hours represents a proportional increase in TBW and may be associated with adverse clinical consequences, such as greater ventilator dependence, impaired cardiovascular function, and disturbances in electrolyte homeostasis. Even when the patient is considered euvolemic, the contributions to volume from nutrition support are generally limited to approximately 25 mL per kg per day, as other reasons for fluid administration are usually indicated.

Depending on the volume assessments by the primary care team, the amount of nutrition support that may be provided by either PN or EN may be affected. The most significant effect occurs when volume restrictions are imposed. When this happens, hypocaloric nutrition is usually provided due to the limitations associated with caloric density. Caloric or macronutrient density is the sum total of calories from protein, carbohydrates, and fat, expressed in kilocalories per milliliter (kcal per mL). Generally, the caloric density of typical formulations routinely prescribed for either PN or EN support is approximately 1 kcal per mL, but special forms of each therapy are available that reasonably allow up to 1.5 kcal per mL to be formulated. However, most enteral formulations are commercially available in fixed concentrations and therefore are less easily manipulated to the specific needs of the critically ill patient than with the PN admixture. For example, with a 1,000 mL fluid restriction allotted for PN support, the increased macronutrient density could be achieved to attain eucaloric nutrition for adult patients weighing up to 60 kg (25 kcal per kg). Of course, these special dosage forms are generally more expensive than conventional products, and the cost-to-benefit ratio has not been fully demonstrated. The usual parenteral formula provided when fluid restriction is necessary is a more standard PN admixture [66], providing 70 g of amino acids and 210 g of glucose (A7D21) approximating 1,000 kcal in a 1 L final volume when

TABLE 191.4

HYPOCALORIC 1,000 mL TOTAL PARENTERAL NUTRITION REGIMENS AS A SINGLE- VERSUS MIXED-FUEL SYSTEM IN INTENSIVE CARE UNIT PATIENTS

Weight (kg)	Total kcal/d[a]	Single-fuel		Mixed-fuel		
		Amino acids[b] (%)	Glucose[c] (%)	Amino acids (%)	Glucose (%)	Lipids[d] (%)
40	600	40 g or 266 mL (4)[e]	128 g or 183 mL (12.8)[e]	40 g or 266 mL (4)[e]	75 g or 107 mL (7.5)[e]	20 g or 100 mL (2)[e]
50	750	50 g or 333 mL (5)[e]	160 g or 228 mL (16)[e]	50 g or 333 mL (5)[e]	96 g or 137 mL (9.6)[e]	24 g or 120 mL (2.4)[e]
60	900	60 g or 400 mL (6)[e]	192 g or 275 mL (19.2)[e]	60 g or 400 mL (6)[e]	115 g or 164 mL (11.5)[e]	29 g or 145 mL (2.9)[e]
70	1,050	70 g or 466 mL (7)[e]	224 g or 320 mL (22.4)[e]	70 g or 466 mL (7)[e]	135 g or 192 mL (13.5)[e]	34 g or 170 mL (3.4)[e]
80	1,200	80 g or 533 mL (8)[e]	256 g or 366 mL (25.6)[e]	80 g or 533 mL (8)[e]	154 g or 220 mL (15.4)[e]	39 g or 195 mL (3.9)[e]

[a]Calories from the hypocaloric regimen consists of 1 g/kg/day of protein and 15 kcal/kg/day total or approximately 50% to 60% of needs. Hypocaloric regimens that are intended as permissive underfeeding are often intended for patients whose present weight is within 10% of ideal body weight.
[b]Assumes a stock bottle of 15% amino acids at 4.1 kcal/g.
[c]Assumes a stock bottle of 70% hydrated dextrose at 3.4 kcal/g.
[d]Assumes a stock bottle of 20% lipid emulsion at 9 kcal/g and providing approximately 20% of total calories.
[e]Final concentration of nutrient in 1,000 mL of total parenteral nutrition fluid.
From Driscoll DF: Formulation of enteral and parenteral mixtures, in Pichard C, Kudsk KA (eds): *Update in Intensive Care Medicine*. Brussels, Springer-Verlag, 2000, pp 138–150, with permission.

compounded from the standard 10% amino acid (700 mL) and 70% dextrose (300 mL) stock solutions, and is usually given for short periods of up to 10 days. Such a formula offers a compromise of the usual desired protein and caloric goals and may provide for a clinical outcome not distinguishable from higher protein, eucaloric regimens [67]. Tables 191.4 and 191.5 provide examples of PN formulations that may be used in the acute critical care setting in adult patients who are fluid restricted (i.e., 1,000 mL for TPN), whose regimens are often hypocaloric for clinical and practical reasons (see Table 191.4), as well as for goal amounts of nutrients in TPN in the absence of fluid restrictions [68]. A recent analysis of highly concentrated TPN admixtures, using a 16% crystalline amino acid solution containing lipid injectable emulsions in eucaloric amounts, showed them to be stable for up to 30 hours with a net fluid savings of approximately 20% compared with conventional 10% amino acids [69]. Patient-specific PN therapy for pediatric patients (premature, neonate, infant, and adolescent) may be devised using specific practice guidelines [70].

Electrolytes

There are seven key electrolytes that must be monitored and provided as necessary in nutritional admixtures. In some cases, certain electrolytes must be given in *standard* quantities as part of the recommend dietary allowance, while others are given in *variable* amounts and replaced according to the clinical needs of the patient. However, in both cases, the daily requirements can be highly variable especially during acute illness for a variety of reasons, including drug therapy [71,72]. As well, in all cases certain electrolytes may be deliberately omitted because of retention disorders associated with certain disease states. This, of course is more difficult to accomplish with enteral formulas that contain fixed amounts of nutrients and electrolytes. Nevertheless, avoiding the consequences of wide fluctuations in serum electrolyte concentrations that may assume clinical significance in the critical care setting is an important and necessary goal.

TABLE 191.5

EUCALORIC, EUVOLEMIC TOTAL PARENTERAL NUTRITION REGIMENS AS A SINGLE- VERSUS MIXED-FUEL SYSTEM IN INTENSIVE CARE UNIT PATIENTS

Weight (kg)	Total kcal/d[a]	Single-fuel		Mixed-fuel		
		Amino acids[b]	Glucose[c]	Amino acids	Glucose	Lipids[d]
40	1,000	60 g or 400 mL	222 g or 317 mL	60 g or 400 mL	166 g or 237 mL	21 g or 105 mL
50	1,250	75 g or 500 mL	277 g or 396 mL	75 g or 500 mL	208 g or 297 mL	26 g or 130 mL
60	1,500	90 g or 600 mL	333 g or 476 mL	90 g or 600 mL	250 g or 357 mL	31 g or 155 mL
70	1,750	105 g or 700 mL	388 g or 554 mL	105 g or 700 mL	290 g or 414 mL	37 g or 185 mL
80	2,000	120 g or 800 mL	444 g or 634 mL	120 g or 800 mL	333 g or 476 mL	42 g or 210 mL

[a]Calories from the eucaloric and euvolemic regimen consists of 1.5 g/kg/day of protein and 25 mL/kg/day respectively. Eucaloric and euvolemic regimens are in conformance with the ASPEN Guidelines for safe total parenteral nutrition formulations and intended for patients whose present weight is within 10% of ideal body weight.
[b]Assumes a stock bottle of 15% amino acids at 4.1 kcal/g.
[c]Assumes a stock bottle of 70% hydrated dextrose at 3.4 kcal/g.
[d]Assumes a stock bottle of 20% lipid emulsion at 9 kcal/g and providing approximately 25% of total calories.
From Driscoll DF: Formulation of enteral and parenteral mixtures, in Pichard C, Kudsk KA (eds): *Update in Intensive Care Medicine*. Brussels, Springer-Verlag, 2000, pp 138–150, with permission.

Standard Additives

Calcium. Approximately 98% of total body calcium is present in the skeleton. Thus, the extracellular concentration in plasma is but a fraction of total calcium stores and is tightly regulated by parathyroid hormone. As absorption of calcium from the gastrointestinal tract diminishes because of impaired absorption or decreased or absent intake, and serum levels begin to fall, the parathyroid glands sense these changes and secrete parathormone that promotes calcium mobilization from bone to restore normal serum concentrations. However, critical illness disturbs normal calcium homeostasis and mild depressions of total and free calcium concentrations are common [73]. The parenteral equivalent of the recommended dietary allowance (pRDA) for adults is about 25% of the oral recommended dietary allowance (RDA) or 200 mg (10 mEq or 5 mmol) of elemental calcium daily. Higher amounts may be used if needed when seeking to maintain calcium at the lower limit of normal, but this does increase the risk of incompatibility with phosphate salts that could produce fatal pulmonary emboli [74–76]. Therefore, if higher amounts are needed, it may be necessary to use fat emulsion-free formulas that allow greater amounts of calcium and phosphate to be infused safely. The other alternative, separate infusions of calcium should be done with great care especially if given by the peripheral veins, as extravasation injury can be severe [77–79]. In addition, the separate administration of parenteral calcium may be incompatible as a coinfusion with other common infusions applied in the critical care setting such as sodium bicarbonate. Moreover, if parenteral calcium is given intermittently and the same intravenous line is to be used for other medications, it should be flushed with saline or other suitable parenteral fluid (i.e., D_5 W) immediately following termination of the calcium infusion. Parenteral forms of calcium are commercially available in three forms, including the gluconate, acetate, and chloride salts. Of these, the gluconate form is preferred in PN admixtures, as it is least capable of forming insoluble products. However, for immediate delivery of calcium in emergency situations such as severe hypocalcemia, the chloride form is the best form for bioavailability reasons, although it is the most reactive salts with respect to compatibility with nutrient formulas and therefore should not be employed when compounding TPN formulas.

Magnesium. Another predominant intracellular cation, magnesium, plays a pivotal role in calcium metabolism. For parathyroid hormone to be secreted in response to hypocalcemia, magnesium is required [80]. In certain instances, corrections of serum magnesium concentrations have been sufficient to normalize hypocalcemia [81]. Such responses have been viewed as an indication of the extent of magnesium deficiency [82]. Furthermore, similar to calcium, hypomagnesemia is commonly seen in critical illness, and the goal is similar (i.e., to maintain levels at about the lower limit of normal). The pRDA is about 33% of the oral RDA or 120 mg (10 mEq or 5 mmol) for elemental magnesium per day. The only parenteral form of magnesium available is as the sulfate salt.

Phosphorus. Phosphorus is an essential element involved in numerous life-sustaining metabolic processes. For example, if omitted from a PN admixture, a life-threatening hypophosphatemia may ensue within days of initiating therapy. Like magnesium and calcium, it is too predominantly found in the intracellular compartment. However, because its gastrointestinal absorption is highly efficient, the pRDA for phosphorus is the same as its oral RDA at 1,000 mg (30 mmol) daily. The use of milliequivalent units to describe phosphorus concentrations in a solution is often mistakenly applied. At this time, the only parenteral form of phosphorus commercially available in the United States is a mixture of inorganic salts of monobasic ($H_2PO_4^-$) and dibasic (HPO_4^-) phosphate ions. Milliequivalents are defined as the molecular weight (in mg) divided by the valence of a single ion, which is determined by the pH of the final solution. As the pharmaceutical dosage form is a mixture of two ions and has a finite yet variable pH range, the dosage form cannot be accurately described in mEq units. However, because sodium and potassium are the accompanying anions, it has become traditional to order them in terms of mEq units where, for example, 30 mmol of phosphorus is found in about 40 mEq of the commonly available formulations.

Variable Additives

Sodium. Sodium is often prescribed in daily amounts ranging from 60 to 100 mEq each day. However, certain clinical conditions preclude the use of sodium beyond minute quantities (i.e., 0 to 20 mEq per day) such as found with florid congestive heart failure, end-stage liver disease, and during attempts to reduce massive volume overload characterized by extensive third-spacing of fluids by volume restriction and active diuresis. In contrast, patients with severe sodium deficits can require daily amounts that may be as much as three to four times higher than typical quantities given to those without sodium restrictions. There is limited to no impact of sodium amounts on nutritional efficacy. Parenteral forms of sodium are available as chloride, acetate, and phosphate salts.

Potassium. Potassium is often prescribed in daily amounts ranging from 40 to 80 mEq each day. As described earlier, there are extreme clinical conditions that may require either severe restriction or expansion of the daily dose so that ranges of potassium intake may be from 0 to 400 or more mEq per day. For instance, a severe amphotericin-induced renal loss of potassium of 100 mEq per L with a 4 L urine output can be managed by placing an equivalent amount in the parenteral formula so long as close monitoring of potassium in the serum and urine output is provided. In all cases, serum potassium concentrations should be closely monitored, as the safe clinical range is narrow and levels outside may produce severe and even life-threatening cardiovascular complications. Like sodium, parenteral forms of potassium are available as chloride, acetate, and phosphate salts.

Chloride. Chloride salts are widely used in nutrition support. Most often they are provided as sodium and potassium salts and quantitatively constitute the majority of anions present in nutritional formulations. In the past, an emphasis on chloride salts with parenteral crystalline amino acid formulations had tended to produce an iatrogenic metabolic acidosis. However, these formulations have since been revised and balanced with an appropriate amount of acetate ions. Thus, it is not necessary to include the inherent concentrations of chloride and acetate present in amino acid products in the additive calculation for the final PN admixture.

Acetate. Acetate salts are primarily used when clinically indicated for the treatment of metabolic acidemia. They are the only suitable alkalinizing salt for use in nutritional formulations. With respect to alkalinizing power, acetate is equivalent to bicarbonate, but this requires cellular metabolism to be effective. Bicarbonate salts should never be used in PN admixtures as they can form insoluble carbonates with calcium ions that are present in most nutritional admixtures and as such could result in the formation of fatal pulmonary emboli [83].

Trace Minerals

To provide a balanced nutritional formulation, trace minerals are generally included in most nutritional formulations. These

include chromium, copper, manganese, selenium, and zinc. In addition, iodine, and molybdenum may also be present in certain formulations. However, for most acute situations, the absence of trace minerals for brief periods (days to weeks) will not produce clinically significant adverse effects. In contrast, the absence of trace minerals in the patient receiving long-term PN support may lead to significant deficiency [84]. However, since manganese is excreted in bile, there is some concern about manganese overload when chronically provided to patients receiving long-term home TPN. Iron is a special case, since hypoferremia is an invariable consequence of the systemic inflammatory response. Furthermore, large amounts of parenteral iron supplementation may worsen septic states. For this reason, iron is not usually provided in TPN formulas during critical illness and when provided to nonseptic patients in home, PN should only be provided when clinically necessary, since iron overload can result in patients with short gut syndromes who have substantial enteral intake. Iron is incompatible in fat emulsion-containing formulas.

Vitamins

Multivitamins are an essential component of all nutritional formulations. This is particularly true for PN formulations. During the national vitamin shortage that occurred in the summer of 1988, three patients died as a result of receiving vitamin-free PN in a matter of 3 to 5 weeks [85]. Ultimately, the cause of death was related to acute thiamine deficiency producing a refractory lactic acidosis. As a water-soluble vitamin, thiamine is an important cofactor in the entry of pyruvate into the Krebs cycle as well as facilitating the processing of glucose within the Krebs cycle. In the absence of thiamine, pyruvate cannot enter the Krebs cycle and is therefore converted to lactic acid. The administration of hypertonic dextrose, the major energy component of PN therapy, accelerates the consumption of thiamine and thus accentuates the clinical course of the condition. Therefore, multivitamins are an essential part of any nutrition support regimen.

The Food and Drug Administration has mandated a change in the composition of adult parenteral multivitamins after nearly 30 years of clinical use [86]. The concentrations of four vitamins (thiamine, pyridoxine, ascorbic acid, and folate) were increased by 50% to 100% of previous amounts and for the first time, vitamin K has been added at 150 mcg per vial. This latter addition may well have some impact on therapeutic doses of warfarin for full anticoagulation as well as for low-dose warfarin therapy for home TPN patients. Lastly, with respect to enteral feeding formulas, the RDA for vitamins is generally met when caloric intakes are between 1,500 to 2,000 kcal per day.

Immunonutrients

There have been a number of nutritional additives that have been alternatively given in supraphysiologic amounts in an effort to improve outcome. The main ones would include lipids composed of high concentrations of the unsaturated long-chain fatty acids (LCFA) containing n3 or n9 fatty acids, medium-chain saturated fatty acids (MCFA), and certain "conditionally essential" amino acids. Historically, soybean oil, containing polyunsaturated fatty acids (PUFAs), rich in the 18-carbon essential (cannot be synthesized endogenously) n6 fatty acid linoleic acid and n3 fatty acid alpha linolenic acid, has been the main source of fat used in lipid injectable emulsions. These fatty acids are the precursors to the true "necessary" fatty acids, arachidonic and eicosapentaenoic acids from the n6 and n3 families, respectively, whereas the n9 fatty acid, oleic acid is nonessential (i.e., can be synthesized endogenously) [87].

Unfortunately, however, the n6 fatty acids from soybean oil can be proinflammatory and potentially detrimental when provided in large amounts to the critically ill, especially in patients with adult respiratory distress syndrome [29,44–45,88–92]. Therefore, substitution of a portion of the conventional n6 fatty acids with alternative lipid fuels such as the n3 fatty acids (20- and 22-carbon PUFAs) from fish oil, or 18-carbon monounsaturated n9 fatty acids from olive oil, or saturated MCFAs from coconut oil (mostly comprises 8- to 10-carbons), may modulate the proinflammatory response. Thus, one benefit of these alternative lipid sources is a reduction in the intake of the highly vasoactive n6 PUFA precursors to ones with less pronounced effects on eicosanoid metabolism by changing the fatty acid composition of cell membranes. The n6 PUFAs produce proinflammatory eicosanoids (i.e., prostaglandins, prostacyclins, thromboxanes, leukotrienes) and increase the responsiveness of cytokines (i.e., interleukin [IL]-1, IL-6, and TNF) which subsequently lead to an increased systemic inflammatory response. Meanwhile, the n3 and n9 lipids lead to eicosanoids that are less proinflammatory and even antiinflammatory. Another benefit is related to a unique metabolic action of the substituted lipid(s) that may have favorable clinical implications. In the case of MCFAs, their metabolism is independent of carnitine transport into the mitochondria with rapid oxidation and less interference with the reticuloendothelial system (RES), while olive oil may be better tolerated with respect to liver function in certain patients receiving conventional soybean oil–based formulations [93].

Of the amino acids used in clinical nutrition, arginine and glutamine have been shown to exert favorable immune effects in patients receiving nutrition support. Arginine has been shown to stimulate T-cell function and wound healing, but may be harmful in certain patients under certain conditions depending on dose [94,95]. Thus, its role in immune enhancement has not been clearly defined, and it is most often given as part of a complex nutritional formula containing other potential immunonutrients. Nonetheless, there appears to be a correlation of demonstrable benefits at doses exceeding 4% of the total energy intake [95]. Glutamine is the most abundant amino acid in the human body, and it is an important nutrient for rapidly dividing immune cells such as lymphocytes and macrophages. Despite its abundance, serum and tissue glutamine concentrations fall during critical illness, which largely reflects its diverse needs during acute metabolic stress. Its role in clinical nutrition is also not well defined, and in a large clinical trial in ICU patients, no differences in outcomes were noted between groups receiving 20 g per L versus a conventional enteral formula that was isonitrogenous and isocaloric [96]. Data with parenteral glutamine tend to be more positive in the critically ill, which may reflect the prominent first pass clearance of enteral glutamine limiting systemic appearance of the amino acid.

DIFFERENCES BETWEEN ENTERAL AND PARENTERAL NUTRITION

Nutrition support may be provided in a variety of ways ranging from noninvasive approaches such as dietary counseling for food and oral supplements to invasive forms of therapy. Of the interventional approaches to nutrition support, these can be accomplished by aseptic placement of intravascular catheters (i.e., PN), or by extravascular devices placed into the gastrointestinal tract (i.e., EN). Each invasive form of nutrition support

has its advantages and disadvantages, and the selection of either approach must be individualized.

Routes of Administration

Enteral Nutrition Options

Like PN therapy, EN can be delivered in a variety of ways with some distinct advantages of one access route over the other. The options include gastric, duodenal, and jejunal placement of various enteral feeding catheters. The simplest technique is the nasogastric placement of a feeding tube into the stomach. However, this approach is often associated with the greatest degree of gastrointestinal intolerance. A higher degree of successful feeding is likely with fluoroscopic, endoscopic, or surgical placement of the feeding catheter beyond the ligament of Treitz. Furthermore, enteral feeding catheters placed in the upper jejunum may even allow feeding in patients with severe pancreatitis [97]. However, placement of feeding tubes in the jejunum postinjury rarely occurs spontaneously and generally requires fluoroscopic or endoscopic assistance, which is expensive and delays feeding.

Parenteral Nutrition Options

PN may be provided by either peripheral or central venous access. Peripheral venous access is clearly less invasive and has minimal complications. The most significant complications are related to maintenance of the patency of the venous catheter and thrombophlebitis and the limited use of each venipuncture site for a relatively short duration. Most peripheral vein catheters will last between 48 to 72 hours from the time of the initial insertion, and therefore a systematic rotation of other infusion sites must be performed. Ultimately, however, the number of viable peripheral venipuncture sites is limited and generally of little practical value in the ICU setting. Moreover, due to the osmolarity limits of these low-flow blood vessels, very large fluid volumes are required to approach protein and energy requirements for most patients, which is not practical in the ICU setting. Peripherally inserted central (venous) catheters (PICCs) generally last longer and can even be used to provide hypertonic PN admixtures. However, the inability to change catheters over guidewires for PICCs for suspected infections, and a greater likelihood of mechanical complications makes this a less desirable alternative to a central venous catheter.

By far, central venous catheterization is most commonly used to deliver PN therapy. Invariably, central venous access is necessary for virtually all patients requiring ICU care, so the delivery of PN therapy does not introduce unique clinical risks associated with catheter placement (i.e., pneumothorax, catheter malposition, catheter infections, and so forth). In addition to supplying nutrition support, the PN admixture can also be used as a vehicle to provide intensive metabolic support such as replacement of large amounts of electrolytes and correction of acid–base balance, which otherwise could not be accomplished by peripheral vein or EN therapy, largely due to osmolarity limitations. Moreover, it has also been used as a vehicle for selected pharmacotherapies, which can also assist in reducing excess fluid intakes associated with multiple diluents (i.e., D_5W, saline, and so forth) used to deliver drugs [98].

Parenteral Versus Enteral Nutrition and Complications

Approximately 15 years ago, there was a significant push toward the use of EN over PN as being a safer mode of nutrient supplementation. The principal benefit purportedly associated with the use of EN is reduced infectious complications compared with PN support in the critically ill. Three key investigations conducted in trauma patients were largely responsible for promoting enteral over PN, showing that patients receiving the latter mode of nutrition support had significantly higher rates of infectious complications [99–101]. In addition, this association appeared to be subsequently confirmed by meta-analysis [102]. However, as eloquently pointed out by Jeejeebhoy [103] in 2001, studies such as these are significantly flawed in that the groups receiving PN have significantly higher energy intakes that are associated with significantly higher blood glucose levels, which predisposes them to nosocomial infections. Higher energy intakes are easily obtainable via PN, whereas they are more difficult to achieve with EN during acute illness due to gastrointestinal intolerance [104].

Subsequently, Simpson and Doig [105] conducted a more sensitive approach to meta-analysis comparing studies of parenteral versus EN only in the critically ill. Previous systematic reviews of the risks and benefits of nutrition support have relied on a composite scales technique that combines certain dimensions of the quality of the selected trial used in the metaanalysis into a combined summary score. Consequently, important differences in methodologic quality (i.e., concealment of allocation, appropriate blinding, and analysis according to the intention-to-treat principle) may be overlooked, making well-conducted studies appear poorly conducted [106]. In contrast, the approach by Simpson and Doig in assessing parenteral versus EN, using the intent-to-treat principle, applied a component scale technique and demonstrated increased infectious complications with PN, but more importantly, reduced mortality by 50% compared with enteral feeding. This impressive benefit was also shown to be largely the effect of early feeding, since a post hoc analysis of TPN versus early enteral feeding showed no difference in mortality [105]. The latter finding was in contradistinction to previous analyses applying the composite scales approach in assessing the benefits and risks of PN [102,107]. Finally, the seminal publication by Van den Berghe et al. [108] in 2001 showed a significant morbidity and mortality benefit in surgical ICU patients receiving adequate nutrition either enterally, parenterally, or by combination when blood glucose levels were aggressively managed with the intravenous infusion of insulin, and the clinical significance of hyperglycemia in nutritional support was clearly established. Two groups of patients were studied ($n = 1{,}548$) to receive either "intensive" or "conventional" insulin therapy concurrent with PN. Blood glucose management assigned to the "intensive" insulin therapy group was treated with an insulin infusion if levels were above 110 mg%, whereas in the "conventional" insulin therapy group, insulin was initiated at levels above 215 mg%. The standard infusion consisted of 50 units of insulin in 50 mL of 0.9% sodium chloride solution (1 U per mL), and the maximum insulin dose was arbitrarily set at 50 U per hour for all groups. Hypoglycemia was defined as a blood glucose determination of 40 mg% or less. Within 24 hours, on average, all patients received approximately 1 g of protein and 19 kcal per kg per 24 hours, respectively. Significant reductions in in-hospital morbidity (e.g., renal and hepatic function, bloodstream infections, polyneuropathy) and mortality were observed in the "intensive" versus "conventional" insulin therapy group, where, for example, control of the morning blood glucose levels for all patients were significantly different between groups (103 ± 33 mg% vs. 153 ± 19 mg%, respectively). Additional significant clinical benefits (e.g., days on ventilator, lower TISS-28 scores) were also noted for those patients with ICU stays exceeding 5 days.

A follow-up study by Van den Berghe et al. [109] in 2006 was conducted, but this time it was performed in medical ICU patients receiving EN. Unfortunately, the nutrition support data were not as clearly presented as in the 2001 study,

but inferences are made as to how it was supplied. The nutritional goals stated from the outset was 22 to 30 kcal per kg per 24 hours (with approximately 20% to 40% of energy as fat calories) and protein at between 0.5 to 1.5 g per kg per 24 hours, with EN beginning as early as possible, once the patient was hemodynamically stable. Subsequently, in the results, two figures are shown that give more details about the success of achieving the stated nutritional goals during this study. One depicts the "total intake of nonprotein calories (kcal per 24 hours)" versus "day" showing that by days 3 and 4 of the study a steady amount of calories (between approximately 1,500 to 1,600 calories per day) were achieved over the 14-day profile. The other depicts the "fraction of kilocalories administered by enteral route" versus "day" showing achievement of 50% of total calories via EN at day 7 and roughly 70% by day 12 of the 14-day profile. The slow progression of enteral nutritional support is expected in critically ill patients, as contrasted from their previous PN study showing rapid advancement of protein and calories [108]. No significant improvements in mortality were noted, but morbidity (e.g., acute renal failure, days on ventilator) was reduced for patients receiving "intensive" insulin therapy. Of note, for the patients staying in the ICU for less than 3 days (n = 433) ("and for whom data were censored after randomization") [109], 56 deaths occurred in the "intensive" versus 42 deaths in the "conventional" insulin infusion group. Moreover, although the severity of hypoglycemia was similar between groups, hypoglycemia was more common in the "intensive" insulin treatment group. A subsequent logistic regression analysis revealed hypoglycemia to be an independent risk factor for death, prompting the investigators to speculate "that the benefit from intensive insulin therapy requires time to be realized" [109]. For patients staying 3 days or more, the mortality benefits seen in the previous study [108] were similarly observed and may support their theory of a time-dependent benefit of aggressive blood glucose management. From a nutritional perspective, the slow progression of protein and calories via the enteral route suggests significant caution in applying aggressive insulin therapy in medical ICU patients receiving EN support only, since parenteral glucose may make hypoglycemia less likely.

A closer evaluation of the manuscript and the table provided in a supplemental appendix reveals that rather marginal amounts of protein and adequate calories were given to the "intention-to-treat group (n = 1,200)" at approximately 40 g of protein and 1,200 kcal daily, whereas in the "long-stayers (in ICU 3 days or more)," approximately 50 g of protein and 1,500 kcal daily were given. It is also obvious from this table that the parenteral infusions were glucose only and not TPN, and that the protein intake in the first 72 hours was about 10 g protein per day. Thus, these critically ill patients did not receive early, adequate feeding, which should be the goal in the critically ill. Furthermore, this less than optimal nutritional therapy was provided at a rather high cost in terms of hypoglycemia with an incidence of 25.1% versus 3.9% in the intensive versus conventional treatment in the long stayers in the ICU.

In conclusion, much of the increase in morbidity related to PN and EN is due to hyperglycemia, which can be significantly reduced by intensive insulin therapy. The level of glycemia necessary to accomplish this goal, whether < 110 mg per dL or only < 150 mg per dL, is not yet defined. Surgical patients being adequately fed may benefit from the lower range, but a recent large study of intensive insulin therapy alone without full feeding in mixed populations of medical and surgical patients have significantly lower mortality with looser control of < 180 mg per dL versus tighter control (81–108 mg per dL) [110]. A possible interpretation is that to accomplish early, adequate feeding requires some parenteral feeding in many critically ill patients who also may serve to minimize the risks of hypoglycemia when employing tighter glucose control.

Tolerance

Enteral Nutrition

Tolerance to nutrition support interventions is highly variable and principally depends on the clinical condition of the patient and the mode of administration. In general, critically ill patients are least able to tolerate all forms of nutrition support. This is particularly true with EN and often limits the amount of protein and calories that can be provided, as gastrointestinal intolerance to feeding is common. As well, a number of other factors associated with ICU care can also interfere with its efficacious delivery [111]. The use of specialized formulations that provide elemental forms of the macronutrients, or are of reduced osmolarity, or of low fat content, may reduce the degree of gastrointestinal intolerance. Moreover, the use of antimotility agents will benefit some patients as well. Nevertheless, despite these preventive measures, gastrointestinal intolerance cannot be successfully managed in all patients. Other maneuvers, such as diluting the enteral feeding formula rarely alleviate the problem and generally should not be undertaken. Rather, providing monomeric or oligomeric formulations with reduced fat content at full strength, given at low rates (i.e., 20 mL per hour) and slowly advanced (i.e., 10 mL per hour every 6 to 12 hours as tolerated) will define those patients who will likely succeed with EN. As a general rule, patients who suffer multiple trauma excluding head injury are usually more tolerant of enteral feeding and allow quicker advancement than those critically ill patients who have closed head injury, sepsis, or are postoperative. Consequently, the time course to achieve eucaloric nutrition is usually longer than with PN.

Parenteral Nutrition

In contrast, patients receiving PN will physically tolerate large amounts of nutrients when given by intravenous administration. The "physiologic brake" that obviously limits EN is not readily apparent. Metabolic abnormalities, such as hyperglycemia and electrolyte and acid–base disturbances, can be easily ascribed to the consequences of the metabolic response to injury, rather than recognizing the contribution of overly aggressive PN support. Furthermore, these iatrogenic metabolic abnormalities are often addressed independently from the PN admixture, such as by separate infusions of insulin, fluid, electrolytes, and so forth, without modifying the PN regimen. The net effect of parenteral overfeeding can unnecessarily complicate the critical care of such patients and lead to significant increases in morbidity and even mortality. However, once metabolic homeostasis is achieved, the time course to reach eucaloric nutrition support is usually brief compared with EN therapy.

Fixed Versus Variable Amounts of Nutrients

Enteral Nutrition

There is limited opportunity to manipulate the contents of EN formulations as these products are premade as "complete" commercial products. Of course, they may be modified by the addition of various nutrient modules, but cannot easily be specifically tailored to the patient, especially during acute illness. For example, a number of electrolyte additives may precipitate the complex feeding formulas and cause clogging of the feeding tube. The addition of other components to the enteral formulation increases the osmolarity, which is an important consideration for enteral feeding, as well as increasing the risk of incompatibilities [68]. Thus, the flexibility of enteral therapy is limited, which may make it difficult to achieve the proper

balance of nutrients during severe metabolic stress. Once the stress response remits and major organ function improves, this becomes a less pressing concern.

Parenteral Nutrition

Major stability issues associated with PN admixtures preclude the manufacture of ready-to-use commercial products. Of these, the interaction between certain amino acids with dextrose forming oxidized end products, known as the Maillard reaction is generally acknowledged [70]. The use of multicompartment bags offer a possible alternative to these reactions, but as with enteral products, they too become clinically limiting in the unstable patient in the acute care setting. Thus, PN admixtures are most often made extemporaneously from individual commercial ingredients (i.e., amino acids, dextrose, lipids, electrolytes, and so forth) by qualified pharmacy personnel. The introduction of automated compounding devices and their subsequent widespread use has made the practice of patient-specific admixtures a relatively easy task [112]. Thus, even the sickest of ICU patients can receive some form of nutrition support by the prescribing of unique and specifically designed formulations to support the protein synthetic response to injury.

Costs

Enteral Nutrition

Historically, EN formulations have been a fraction of the cost of PN admixtures as they are ready-to-use and largely comprised of polymeric forms of macronutrients. However, with refinements in these products to construct oligomeric or monomeric forms of protein and carbohydrates, the so-called elemental formulas, the costs have increased substantially. Moreover, the addition of novel nutrients, such as omega-3 fatty acids, glutamine, arginine, and others to produce nutritional supplements that may have pharmacologic effects, particularly with respect to immune function, has increased costs that now exceed most PN formulations per kcal. Although the data are promising for these innovative formulations in terms of their potential to reduce length of stay and possibly infectious complications, the full extent of these claims have not been fully substantiated.

Parenteral Nutrition

By historical comparison, PN was always more expensive than EN therapy. There were many good reasons for this [113], considering the product had to be specially compounded under aseptic conditions to be suitable and safe for intravenous administration. As the methods of commercial production improved and became more efficient and competition increased, the costs of PN therapy have significantly declined. Compared with specialized formulas that contain immunonutrients or certain concentrated enteral products, the present costs of PN therapy are equal or in many cases less expensive. In contrast, for conventional, polymeric EN supplements, the cost of the formulations is still substantially less than PN formula costs. However, the placement of an enteral feeding tube and components (pumps, sets, and so forth) are dedicated to the provision of nutrition support, whereas central venous lines are already being used for the provision of intravenous fluids, medications, and blood tests. Therefore, additional costs of even conventional EN therapy must be considered.

Complications

The complications or adverse patient events associated with parenteral and EN include mechanical, septic, and metabolic misadventures [114]. For example, mechanical complications of invasive nutrition support are often associated with the misplacement of various types of feeding access devices (i.e., vascular injury or pneumothorax). With experienced clinicians, the incidence of such complications is substantially reduced and clinically acceptable at about 1% to 2%.

Metabolic and associated septic complications are more common and can have a significant impact on patient outcome. Severe disturbances in fluid, electrolyte, and acid–base homeostasis are commonly associated with high rates of morbidity and mortality in the ICU. This is especially true in patients with significant heart disease [115]. As well, septic complications in association with hyperglycemia and infections in critically ill patients receiving parenteral or EN are at least equally significant, if not even more so [116]. Therefore, a more modest provision of energy intake (i.e., approximately 25 total kcal per kg per day) should be the overall goal of therapy by whatever route of delivery and is most likely to succeed, and with this, fewer nutrition-related complications are likely. However in the first 3 to 7 days of enteral and PN providing at least 50% of the estimated energy requirement along with protein intake of at least 1 g per kg may be a reasonable compromise meeting the definition or early, adequate feeding while lowering the risk of metabolic and infectious complications.

Appropriate Application of Nutrition Support

Nutrition support does not improve outcome in operative patients who are well nourished, no matter what route of administration it is given. A number of examples appear in the medical literature supporting this contention. For example, a randomized clinical trial of perioperative nutrition support only found significant improvement in the malnourished group irrespective of feeding mode [117]. Heslin et al. [118] reported no benefit with enteral tube feeding in patients with gastrointestinal cancer without significant weight loss. In fact, the routine provision of EN in well-nourished patients may cause significant impairments in ventilatory function and mobility [119]. Finally, an extensive review of the literature has corroborated the lack of benefits in the standard prescription of nutrition support in patients who initially are well nourished and undergoing moderate stress as following major thoracoabdominal surgery [120]. There is reasonable support for early and adequate feeding in the most critically stressed even when initially well-nourished such as those with closed head injury, severe multiple trauma, major third degree burns, and severe sepsis, not to prevent the development of malnutrition but presumably to limit the severity of the systemic inflammatory response.

In contrast, invasive feeding in the malnourished patient is likely to be effective in a variety of clinical scenarios. This is particularly true during acute metabolic stress, where ongoing catabolism results in significant daily losses of body protein. Patients with weight loss classified as moderate (i.e., 10% or more) or severe (i.e., 20% or more) from usual or IBW are most susceptible to nutrition-related complications such as infection or wound dehiscence. The absence of nutritional intervention in this vulnerable population for protracted periods of time (i.e., greater than 7 to 10 days) may have a significant impact on outcome. Moreover, even the initially well-nourished patient cannot sustain the protein synthetic response to injury for long periods. For example, in a randomized study of the effects on outcome of postoperative feeding with TPN, those who were inadequately fed for 14 days had a significant increase in morbidity and mortality [121]. Patients who suffer multiple traumas, major burns, or closed head injury are a unique group. Although generally well nourished at the outset, the severity of catabolic response and the likely duration

of substantially longer than 7 days make early nutritional intervention within the first few days beneficial.

MONITORING PARAMETERS FOR NUTRITION SUPPORT

Electrolytes

During critical illness, severe electrolyte disorders are common and are primarily the result of various concomitant etiologies, including changes in (a) the function of major organ systems, especially the kidneys; (b) fluid balance affecting intravascular volume and the hormonal milieu produced as a result of the metabolic response to severe stress(es); (c) intra- or extracellular shifts of ions associated with acid–base disturbances; and (d) multiple drug therapies. Renal dysfunction has profound effects on electrolyte balance by influencing the absorption and excretion of most notably, sodium, potassium, magnesium, phosphorus, and titratable acids. As renal function declines, the excretion of these electrolytes decreases and the PN admixture must be adjusted accordingly. For example, in some cases, electrolytes are significantly reduced, while in other circumstances they are entirely omitted from the daily admixture. As well, chloride ions are often substituted with alkalinizing anions such as acetate to combat the metabolic acidosis associated with renal failure.

Fluid overload is a common finding in critically ill patients related to intraoperative support of renal blood flow and function, acute volume resuscitation with crystalloids in the ICU, and the administration of multiple intravenous medications that may produce its own set of complications. For example, acute increases of 10% or greater above usual body weight over short intervals clearly reflect a significant expansion of total body water that may impede the weaning of the patient from mechanical ventilation. Thus, clinical efforts to return to the patient's premorbid weight, such as by aggressive diuretic therapy and concentrating intravenous medications in the least diluent volume possible, are often used. In certain severe circumstances, the use of colloids for acute volume expansion, followed by aggressive diuretic therapy as a "push–pull" method of fostering diuresis is undertaken to achieve a net negative fluid balance. More recently, the use of hemofiltration procedures to accomplish this goal has proven quite effective. Despite "third-spacing" of fluids, the consequences of the antidiuretic and antinatriuretic responses of stress often present as a hyponatremia and can be mistakenly treated by the parenteral administration of sodium salts in an effort to correct the serum sodium concentration. However, given that sodium essentially distributes in total body water, one can easily calculate that, in fact, the patient is both fluid and total body sodium overloaded. Hence, clinical maneuvers to address the problem should be directed at increasing both sodium and free water losses, with gradual restoration of serum sodium concentrations. A clinical example of this estimation appears in Table 191.6.

The acute intra- or extracellular shifting of electrolytes is primarily the result of the effects of changes in acid–base homeostasis and serum insulin concentrations. In the former case, serum potassium concentrations are most affected by changes in acid–base status. Potassium is predominantly an intracellular ion whose concentration in the intracellular compartment is much higher than its extracellular concentration. When arterial pH falls below normal, potassium shifts to the extracellular compartment and hyperkalemia occurs, and conversely, metabolic alkalosis produces hypokalemia.

Insulin also has a profound effect on the shifting of potassium, magnesium, and phosphorus between the intra- and extracellular environments. In fact, the life-threatening refeeding syndrome that occurs in severely malnourished patients is associated with the shifting of these electrolytes from the extracellular to the intracellular compartments [122]. In the atrophic heart muscle characteristic of severe malnutrition (i.e., greater than 30% below ideal body weight), severe reductions of serum potassium (i.e., less than 3 mEq per L) and serum phosphorus (i.e., less than 0.2 mg per L) related to feeding may have life-threatening electrophysiologic consequences [123].

Finally, critically ill patients commonly receive multiple drug therapies intravenously for a variety of clinical reasons and include, for example, cardiovascular agents, vasopressors, diuretics, anesthesia/sedation therapy, crystalloids, colloids, antibiotics, anticoagulants, and so forth. These can cause clinically significant effects by altering intended drug actions (i.e., toxic synergism, reduced drug effects) or by addition of substantial diluent volumes (i.e., greater than 500 mL), worsening a fluid-overloaded state. The clinical care of acutely ill patients with severe fluid and electrolyte disorders can be optimally managed through intensive metabolic monitoring and selective manipulations of PN admixture components [71,72,123].

TABLE 191.6

ESTIMATING TOTAL BODY SODIUM IN THE ACUTE CARE SETTING[a]

Premorbid total body sodium	
Total body water @70 kg	= 42 L
Total body sodium	= 42 L × 140 mEq/L
	= **5,880 mEq**
Present total body sodium	
Total body water @91 kg	= 42 L + (91 kg − 70 kg)
	= 63 L
Total body sodium	= 63 L × 130 mEq/L
	= **8,190 mEq**
Excess total body sodium	
8,190 − 5,880	= **2,310 mEq**

[a]Assumptions: Premorbid weight = 70 kg male; presently = 91 kg; serum sodium = 140 mEq/L (normal); presently = 130 mEq/L; total body water = 60% (for males).

Insulin and Glucose Homeostasis

Notwithstanding its regulatory role in glucose homeostasis in terms of glucose production and breakdown in the liver, as well as its facilitated transport of glucose into muscle and other obligatory tissues, insulin is a complex hormone that exhibits numerous metabolic effects that may be of significant clinical consequences in critically ill. The mechanisms by which abnormally elevated blood glucose concentrations in critically ill patients produce metabolic dysfunction have been described [124]. With respect to infectious risk, the ability of mononuclear (macrophages and monocytes) and polymorphonuclear neutrophils to exert phagocytic, oxidative bursts, and killing functions is significantly impaired. Thus, infections of the bloodstream, lungs, and superficial wounds (i.e., any surgical incision site, intra-, and extravascular catheter sites, or other topical sites of injury) are significantly increased following periods of hyperglycemia.

Glucose homeostasis is best achieved when parenteral insulin is given in an effective manner. A review of the methods of administration employed emphasize that the route of insulin delivery should be commensurate with the means of

administration of carbohydrate calories [125]. In the acute phases of critical illness, patients receiving PN should receive intensive insulin therapy [108]. Once, stabilized (i.e., patients receiving the largest source of glucose as parenteral calories), insulin should be given in the TPN admixture in amounts sufficient to cover the caloric intake from this source over 24 hours. When exclusive PN therapy is given, 24-hour glucose intake may account for as much as 150 to 300 g per L daily (510 to 1,020 kcal), requiring substantial amounts of insulin in the admixture, and can be effectively accomplished [125]. As well, in some cases supplemental "low-volume, full-strength" EN may provide 50 to 150 g per 24 hours (170 to 510 kcal), which should be managed with subcutaneous insulin provided based on blood glucose determinations taken on a regular basis and algorithm-based insulin doses.It should be emphasized that, the insulin should be administered subcutaneously as an intravenous dose has a serum half-life of approximately 5 to 7 minutes. The same principles may be applied to patients receiving substantial amounts of glucose in the peritoneal dialytic regimens, where insulin is often best provided in the dialysis solution. Thus, in some cases, such as a patient undergoing both peritoneal dialysis and PN or EN, insulin is given via multiple routes to cover the administration of glucose from various sources to link the insulin administration to the source of exogenous glucose. When hyperglycemia is severe due to severity of the stress response or severity of insulin deficiency (type 1) or insulin resistance (type 2), it is reasonable to employ continuous intravenous insulin and close blood glucose monitoring to quickly establish glucose homeostasis, whatever the source of exogenous glucose.

Goals of Nitrogen Balance

Achieving positive nitrogen balance is an unrealistic goal in the critically ill early in the clinical course. Rather, the principal aim of nutritional intervention is to support the protein synthetic response to injury and, therefore, narrow the negative nitrogen gap (where output exceeds input) that occurs during severe metabolic stress. Even when the metabolic stress has subsided, it should be recognized that nutritional rehabilitation of the moderate to severe malnourished patient occurs at a limited rate equivalent to approximately 1 kg of body weight per week and generally much of this repletion will occur outside the hospital after discharge. This estimation is based on a maximum rate of repletion of a positive nitrogen balance (i.e., approximately + 5 g per day) that represents 150 g of lean tissue (hydrated protein) and a calorically equivalent amount of fat (13 g) per day. Weight increases above this rate of repletion can only reflect increases in total body water.

Finally, it should be mentioned that when expending the effort to obtain a 24-hour urine collection, additional laboratory measurements should be performed on this specimen such as for the determination of creatinine excretion and certain electrolytes (sodium, potassium, chloride). In this way, important additional clinical information may be provided including creatinine clearance, urea clearance, fractional excretion of sodium, and quantification of electrolyte losses, among other possible data that may be used in the clinical and nutritional/metabolic care of critically ill patients.

EVIDENCE-BASED GUIDELINES FOR NUTRITION SUPPORT THERAPY

In 2009, the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) developed and copublished "Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient" [126,127]. The last statement of the introduction of this document is noteworthy: "*Delivering early nutrition support therapy, primarily using the enteral route, is seen as a proactive therapeutic strategy that may reduce disease severity, diminish complications, decrease length of stay in the ICU, and favorably impact patient outcome.*" Of the 12 categories or conditions (sections A through L), nine sections related to EN, two sections on PN, and one section (L) relating to end-of-life situations. It is the authors' opinion that this document is unfortunately biased against the potential utility of PN in many circumstances. The assessment system applied in the guidelines consisted of "Levels of Evidence" and "Grades of Recommendation." "Levels of Evidence" were from I to V, with "Level I" being the strongest evidence and "Level V" being the weakest evidence. The "Grades of Recommendation" were from A to E, with "A" being the highest and "E" being the lowest. If, for example, one scores the grades according to a quality point average (QPA) as applied in education with A = 4.0, B = 3.0 . . . E = 0.0, the evidence is poor for both EN and PN. For example, in the SCCM/ASPEN 2009 guidelines, the QPA for all EN sections was 1.21 and the QPA for all PN sections was 1.25. We selected three controversial statements in the guideline:

A3. "EN is the preferred route of feeding over parenteral nutrition (PN) for the critically ill patient who requires nutrition support therapy. Grade B"

The statement is correct, and fits Dr. Dudrick's original thesis "if the guts works, use it," but the principal rationale for its preference, that is, reduced infectious morbidity is misidentified. Although previous studies have shown this association to be true, the premise overlooks the importance of blood glucose control and caloric intake in these studies. Invariably, the PN group in many of the supporting studies received significantly more calories than the EN group and consequently, had higher blood glucose values that clearly increase infectious complications. This is not surprising since EN is often not well tolerated in eucaloric amounts as PN, and is frequently interrupted for various clinical maneuvers or diagnostic tests in the critical care setting. As well, the insulin required to maintain glucose homeostasis is greater for parenteral compared to enteral glucose. Furthermore, the data supporting this statement was essentially derived before the subsequent eras of reduced energy provision and tight glucose control in the critically ill.

G1. "If the patient is deemed to be a candidate for PN, steps to maximize efficacy (regarding dose, content, monitoring, and choice of additives) should be used. Grade C"

In accordance with the thesis of "do no harm," it would seem intuitively obvious that the safety and efficacy of PN would be accomplished by optimizing the formulation. A "Grade C" recommendation diminishes the importance of dosing nutrients, which unfortunately, is associated with a long history of overfeeding and its attendant complications. In the same section (G6), the use of extemporaneously prepared parenteral glutamine is given the same "Grade C," despite the fact that such an additive is classified as a "HIGH RISK" compounded sterile preparation by the United States Pharmacopeia [20].

H3. "Serum phosphate levels should be monitored closely and replaced appropriately when needed. Grade E"

The literature is replete with data on the importance of serum phosphate levels is the critically ill, especially with respect to the risks associated with hypophosphatemia on myocardial performance and respiratory function [128]. Moreover, the provision of hypertonic glucose in a PN admixture

produces a supraphysiologic increase in serum insulin levels that will cause significant intracellular shifts that may produce life-threatening hypophosphatemia in susceptible patients. A "Grade E" recommendation is inappropriate in this circumstance. Also in 2009, the European Society of Parenteral and Enteral Nutrition (ESPEN) produced "Guidelines on Parenteral Nutrition: Intensive Care" [129]. Seventeen statements (categories or conditions) are included and there are three Grades of Recommendation (A, B, C) with the strongest evidence being "Grade A" versus the weakest evidence with a "Grade C." Only two statements received "Grade A." We selected three controversial statements in this guideline.

Under "Requirements"

> "During acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease negative energy balance. Grade B"

In the ICU setting, particularly during the early phases of critical illness, hypocaloric regimens often seem to be most prudent. Maintenance of normal blood glucose values should take precedence over energy balance in most critical care settings, and then once achieved, judicious increases in calories can commence.

> "In the absence of indirect calorimetry, ICU patients should receive 25 kcal/kg/day increasing to target over the next 2–3 days. Grade C"

As already stated, caloric intakes in the ICU should be advanced slowly after the initial provision of 50% of energy and 1.0 to 1.2 g protein per kg to avoid hyperglycemia and infectious morbidity. As stated earlier, for most patients, providing 25 kcal per kg per day is sufficient to support the protein synthetic response to metabolic stress. The guideline, as stated, implies that 25 kcal per kg per day is the starting point, when in fact, for most adult patients, it is the target range [130], and is gradually reached after initiating lesser amounts of calories from the outset.

Under "Amino Acids"

> "When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of l-glutamine (e.g., 0.3–0.6 g/kg/day alanyl-glutamine dipeptide). Grade A"

Although there is a commercial product in Europe that is available to provide glutamine supplementation, a recommendation of Grade A seems to be overly optimistic. This is especially true given the recent assessment of l-glutamine in the ICU of an "area of uncertainty" from one of the leading investigators in the field [130]. Thus, such a recommendation seems premature at this time.

At this time, the data is unclear for several reasons. First, the guidelines and methods of assessment must be standardized between organizations. Second, "mining of data" from past studies, many of which are significantly flawed with respect to design and endpoints, cannot yield meaningful guidelines, despite the use of statistical tools, such as meta-analyses. Third, critically ill patients are not homogenous. As recently pointed out, EN is contraindicated in 10% to 15% of ICU patients; there are very few well-designed, randomized controlled studies of PN efficacy, and preexisting malnutrition, combined with numerous pathophysiologic factors in ICU patients which greatly complicate the role of nutrition support [130].

Thus, it seems that to definitively address the evidence for nutrition support therapy in the ICU setting will require designing better studies in the future rather than the current methods to rehash old data from a previous era using statistical tools. A major emphasis should clearly be on the design (randomized controlled trial, sufficient power, APACHE score, etc.) and specific endpoints for future studies to answer the question of the impact of nutritional therapy in the critically ill on morbidity and mortality and clinical outcome. For example, multicenter studies should focus on the potential role of early (within 72 hours of ICU admission) and adequate energy (> 50%, but < 110% of energy requirements) and protein (at least 1.2 g per kg per day) by whatever means necessary (enteral, parenteral, or both). Only then can we have a true understanding of the role of nutrition support therapy in the critically ill.

CONCLUSIONS

Nutritional and metabolic support is an essential component of the clinical care of critically ill patients. However, if applied in an overly aggressive manner without thought to the nutritional status, amounts of nutrients, route of administration, and the clinical condition of the patient, significant iatrogenic complications may occur and little clinical benefit can be expected. Thus, nutritional support of the critically ill must be carefully integrated into the overall clinical care of the patient, with specific and measurable outcome measures in order to obtain the maximum benefits of this important therapy.

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CHAPTER 192 ■ DISEASE-SPECIFIC NUTRITION

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INTRODUCTION

In the critically ill patient, the constant barrage of multiple physiologic derangements quickly leads to malnutrition. The hypermetabolic response to stress changes the nutritional requirements of these individuals, but failure of the various organ systems complicates the issue. Renal, hepatic, and pulmonary function must be considered when prescribing nutritional therapy in the intensive care unit (ICU). This chapter will discuss the metabolic abnormalities associated with these disease processes, the nutritional assessment of the patient in organ failure, and propose evidence-based guidelines for nutritional support in these disease-specific populations.

RENAL FAILURE

Despite many recent advances in medical therapy, management of the critically ill patient with renal failure remains a challenging endeavor. Acute renal failure (ARF) is associated with an overall mortality rate of 50% to 90%, depending on its derivations and comorbid conditions [1]. Hypotension and hypovolemia, secondary to excessive fluid losses, inadequate fluid replacement, or decreased cardiac output are the leading causes of renal failure in the ICU. Factors such as shock or sepsis and exposure to nephrotoxic drugs or blood transfusions can also predispose patients to renal dysfunction. Early diagnosis and restoration of circulating blood volume to the kidneys may decrease the risk of permanent damage; however, the course to renal recovery is often a complicated one. The patient in chronic renal failure (CRF) is also at increased risk for morbidity, as these patients will likely present with protein-calorie malnutrition at baseline. Moreover, the nutritional support of the patient on dialysis will offer a unique challenge to the critical care physician.

Malnutrition and Hypermetabolism

In general, renal failure is characterized by altered nutrient metabolism, defective metabolic waste excretion, inadequate nutrient intake, and excessive nutrient losses. Approximately 10% to 70% of patients with CRF undergoing maintenance dialysis are severely malnourished [2,3]. In these patients, malnutrition is most often the result of poor dietary intake secondary to uremia-induced gastroparesis, poor-tasting highly restrictive diet prescriptions, and medications with gastrointestinal side effects. Diminishing creatinine clearance levels have been linked to a spontaneous decline in the dietary protein intake of CRF patients as well [3,4]. In addition, patients with acute renal failure and critical illness represent by far the largest group receiving supplemental nutrition [5].

The dialysis dose also plays a significant role in the development of malnutrition. The protein catabolic rate of patients undergoing dialysis can be calculated to estimate daily protein intakes of these individuals [6]. In a 1983 investigation by Acchiardo et al., daily protein intakes of less than 0.8 g per kg, as measured by protein catabolic rate, correlated with an increased morbidity and mortality rate compared to patients with greater protein intakes [7]. A subsequent study by Lindsey and Spanner demonstrated a strong linear relationship between dialyzer urea clearance, duration of dialysis, and volume dialyzed (collectively expressed as Kt/V) and protein catabolic rate [8]. It is suggested by this correlation that an adequate dose of dialysis is influential on sufficient nutrient intake and the prevention of malnutrition in chronic dialysis patients [9].

Critical illness imposes an even greater metabolic stress and nutritional demand on the patient with renal dysfunction. Protein-calorie malnutrition (PCM) is reportedly present in 25% to 60% of individuals undergoing continuous renal replacement therapy (CRRT) within the intensive care unit [10]. It is important to note that the increased energy expenditure seen in these patients is a direct result of the hypermetabolic response to infection and injury and not of the renal failure itself. Indirect calorimetry has been used to show that the intensity of renal dysfunction has no direct bearing on energy expenditure [11]. Renal failure is, however, the root of several metabolic alterations that often interfere with nutritional status and overall stability of the critically ill patient.

Metabolic Abnormalities

Common metabolic abnormalities associated with ARF include glucose intolerance, impaired lipolysis, increased protein catabolism, decreased protein synthesis, fluid and electrolyte imbalance, and metabolic acidosis (Table 192.1). Although renal excretion of insulin is diminished, insulin resistance coupled with the stress of sepsis or injury can lead to significant hyperglycemia in this patient population. Decreased activity of lipolytic enzymes, such as hepatic triglyceride lipase and lipoprotein lipase, may reduce clearance of parenterally infused triglycerides by as much as 60% in ARF patients versus controls with intact renal function [12]. Adequate energy provision may thus be hindered by altered carbohydrate and fat metabolism. Nonprotein calorie requirements in ARF patients are best met with formulas providing mixed substrates in the ratio of 50% to 70% as carbohydrate and 30% to 50% as fat [13].

TABLE 192.1

METABOLIC RESPONSES TO ACUTE RENAL FAILURE

Nutrient	Metabolic abnormalities
Glycemic	Diminished metabolism of insulin and glucagon Glucose intolerance (hyperglycemia) Peripheral insulin resistance Increased glycogenolysis and gluconeogenesis
Lipid	Increased lipolysis with reduced clearance of serum lipids Hypercholesterolemia Hypertriglyceridemia
Protein and amino acid	Increased catabolism of skeletal muscle and visceral proteins Diminished amino acid uptake Reduced insulin-mediated protein and amino acid synthesis Azotemia
Fluid and electrolyte	Anuria Anasarca Ascites Altered serum concentrations of sodium, phosphorus, or potassium Hypocalcemia Metabolic acidosis

Data compiled from references [8,12,17,19,26].

Several factors contribute to increased protein catabolism and overall negative nitrogen balance in ARF patients. In accordance with the metabolic response to injury, patients with renal failure experience an increase in gluconeogenesis, leading to the breakdown of skeletal muscle proteins for use as energy and for synthesis of acute-phase proteins. Metabolic acidosis, frequently seen in renal failure, can trigger skeletal muscle protein breakdown as well. Reduction in muscle protein synthesis in this population has been linked to diminished cellular uptake of glucose and amino acids secondary to insulin resistance, altered cellular ion transport mechanisms, and defective intracellular synthesis [14,15].

Varying protein and energy provisions also influence protein catabolism and nitrogen balance in ARF patients. A 1996 investigation of 40 ICU patients with ARF receiving continuous venovenous hemofiltration revealed that at levels of protein administration above 1.5 g per kg per day, increasing energy provisions are associated with an increase in protein catabolism [16] (Fig. 192.1). Increasing energy provisions had a protein-sparing effect at lower levels of protein administration. Net nitrogen balance was also examined in this population (Fig. 192.2). Protein administration rates of 1.5 to 2.0 g per kg per day were associated with a positive net nitrogen balance,

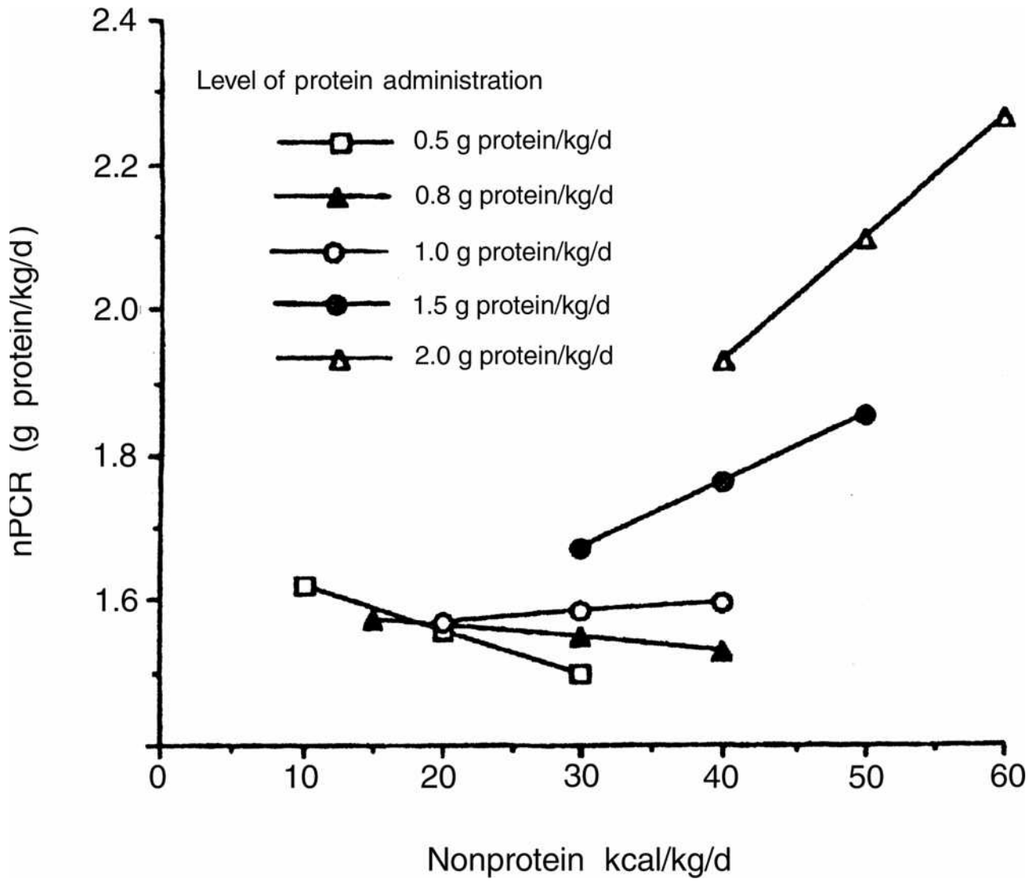

FIGURE 192.1. Effect of varying energy and protein provisions on protein catabolism. At higher levels of protein administration (> 1.5 g/kg/d), increasing energy provisions are associated with increased net protein catabolic rate (nPCR). At lower levels of protein administration (< 0.5 g/kg/d), increasing energy provisions promote protein sparing. [Adapted from the American Society for Parenteral and Enteral Nutrition (ASPEN) and Macias WL, Alaka KJ, Murphy MH, et al: Impact of nutritional regimen on protein catabolism and nitrogen balance in patients with acute renal failure. *JPEN J Parenter Enteral Nutr* 20(1):56–62, 1996, with permission. ASPEN does not endorse the use of this material in any form other than its entirety.]

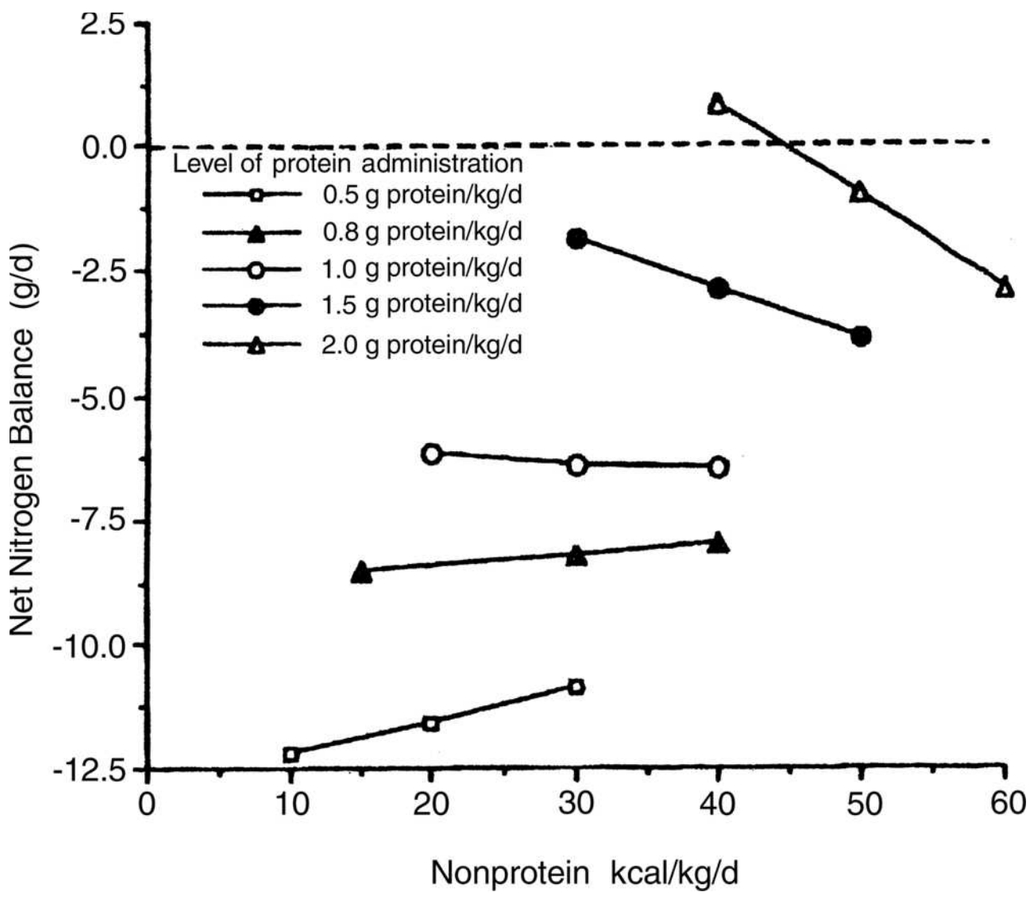

FIGURE 192.2. Effect of varying protein and energy provisions on nitrogen balance. Higher levels of protein administration (> 1.5 g//kg/d) in combination with lower energy provisions (25–35 kcal/kg/d) promote a more favorable net nitrogen balance. [Adapted from the American Society for Parenteral and Enteral Nutrition (ASPEN) and Macias WL, Alaka KJ, Murphy MH, et al: Impact of nutritional regimen on protein catabolism and nitrogen balance in patients with acute renal failure. *JPEN J Parenter Enteral Nutr* 20(1):56–62, 1996, with permission. ASPEN does not endorse the use of this material in any form other than its entirety.]

although at these elevated levels of protein provision, lower-energy administration rates were necessary to prevent protein catabolism and promote more favorable nitrogen balance. Final nutrient recommendations were for 1.5 to 1.8 g protein per kg per day with energy levels between 25 to 35 kcal per kg per day in critically ill ARF patients on continuous venovenous hemodialysis (CVVHD) [5,16].

Close monitoring of fluid status is crucial to the maintenance of adequate intravascular volume and renal perfusion. Fluid is typically restricted to 1.0 to 1.5 L per day in nondialysis anuric or oliguric patients. Concentrated enteral or parenteral formulas are often required to meet daily nutrient needs under these circumstances. Dialysis, with special emphasis on CRRT, allows for a liberalization of fluid provisions to thereby permit an adequate supply of protein and energy to the renal patient. In the ICU setting, ARF patients tend to be severely volume overloaded with fluid shifting to the extravascular space secondary to hypoalbuminemia. Even while on some form of CRRT, maintenance of fluid balance is challenging in these patients and importance should be given to adequate protein provision for repletion and reversal of the effects of low serum albumin levels. In CRRT, there is a loss of at least 0.2 g amino acids per liter of ultra filtrate (up to 10 to 15 g amino acids per day), and of 5 to 10 g per day of proteins. Vitamins are also lost in significant amounts; however, there does not appear to be lipid losses across the filter [5].

Serum electrolyte levels fall within a wide range of highs to lows depending on renal excretion, extent of catabolism, and type and duration of dialysis [17]. Increased catabolism of skeletal muscle protein releases phosphorus, potassium, and magnesium into the bloodstream, leaving elevated serum electrolyte values. Because of this, parenteral nutrition (PN) formulations for renal patients are often made with low levels of these cations. A 1998 case report demonstrated the dangers of undershooting electrolyte needs in a frequently malnourished CRF population [18]. Introducing a carbohydrate load parenterally or even enterally to a malnourished patient stimulates insulin release and cellular anabolism, thereby enhancing intracellular ion transport [19]. The subsequent decline in serum electrolyte levels with resulting clinical complications is referred to as the *refeeding syndrome*. This case study reported four CRF patients who developed significant hypophosphatemia after starting PN due to inadequate electrolyte provisions in combination with intracellular shifts [18]. It is thus recommended that dextrose infusions be started gradually and serum electrolytes be monitored closely to correct for potential abnormalities in this population. Depressed serum ionized calcium levels are a common result of hyperphosphatemia and uremia. Supplementation is most often necessary to prevent release of calcium from the bone. Multivitamin preparations standard to enteral and parenteral formulas are adequate for most ARF and CRF patients. Support exists in the literature that vitamin C should not exceed 30 to 50 mg per day, because inappropriate supplementation may result in secondary oxalosis. If signs of vitamin A or other toxicities are observed, daily provision may need to be withheld. The kidney normally excretes trace elements; however, excess accumulation in renal failure is unlikely as gastrointestinal tract losses also occur. The micronutrient milieu may also be affected by the mode and dose of renal replacement therapy. Recent data show that prolonged CRRT results in selenium and thiamine depletions despite supplementation at recommended amount [5].

Standard daily doses of trace elements may be safely given to most patients in renal failure. Iron deficiency anemia is a commonly documented finding among end-stage renal disease patients. Recent research has focused on anemia and carnitine, an amino acid with a central role in long-chain fatty acid oxidation. Deficiency of carnitine has been associated with dialysis, and supplementation of l-carnitine has led to the improvement

of hematocrit levels in HD patients [20]. Metabolic acidosis in this population is a result of diminished acid excretion, increased protein catabolism, and daily protein intake [21]. Bicarbonate should be given enterally or intravenously to maintain pH more than 7.2 or serum bicarbonate more than 17 mEq per L. When supplementing by PN, sodium or potassium acetate is given because bicarbonate forms an insoluble precipitate with calcium in PN solutions.

Nutrition Assessment

The identification of malnutrition and timely initiation of nutrition support in critically ill patients with renal failure may not only reduce their degree of protein depletion but also increase their chances for survival [1]. Unfortunately, common measures of nutritional status, such as serum albumin, serum transferrin, weight changes, and anthropometrics tend to fluctuate with the alterations in fluid balance inherent to this patient population. Despite this, serum albumin is considered the strongest laboratory predictor of mortality for hospitalized patients with renal failure [22]. Daily monitoring of weight and intake and output records can help to assess fluid balance in these individuals. It is essential to use a dry weight (i.e., free of edema or ascites) when examining alterations in weight status. The dry or adjusted body weight of a renal patient may then be used to more closely estimate daily nutrient needs.

Continuous Renal Replacement Therapy (CRRT) Versus Intermittent Hemodialysis (HD)

It is commonly thought that dialysis therapy can be relied on to correct many of the metabolic derangements associated with acute and chronic renal failure. This may be true under most circumstances; however, research and patient care experience have shown that patients receiving intravenous (IV) nutrition are at greater risk for fluctuating serum chemistries despite regular dialysis treatments [1,18]. HD can also increase the risk of hypotension and may add to the hemodynamic instability of the ICU patient by limiting the removal of adequate fluid. CRRT is useful for 24-hour-per-day clearance of nitrogenous wastes, metabolic by-products, and excess fluids. CRRT is often preferable to HD in the critical care setting because it reduces the risks for fluid and electrolyte disorders and hypotension while allowing for more liberal fluid and nutrient provisions. In patients with severe fluid intolerance, slow continuous ultrafiltration may be necessary. Protein losses can be as high as 10 to 13 g per HD session versus 5 to 10 g per day in CRRT [23,24]. Amino acids can be added to the hemodialysate solution to promote retention of nitrogen balance [25]. Consideration should be given to typical glucose content of the dialysate, as this may make a significant contribution to the caloric load of patients already exhibiting some form of glucose intolerance. Dialysate of CRRT is approximately 1.5% glucose, thereby contributing up to 600 glucose calories during a 10-L per day dialysis infusion [26].

Enteral and Parenteral Formulations

A wide array of enteral nutrition products has been designed for patients in varying stages of renal disease (Table 192.2). Formula selection depends largely on the individual's fluid allowance [27]. For predialysis ARF patients in need of short-term enteral nutrition, a formula containing only essential amino acids and histidine with little or no vitamins, minerals, and electrolytes may be appropriate. Products with reduced levels of protein, phosphorus, potassium, magnesium, and vitamin A are useful for patients with chronic renal insufficiency, yet not on dialysis. Moderate protein formulas with low electrolyte content are often indicated for patients receiving intermittent dialysis treatments. All enteral products designed for use in renal dysfunction are concentrated in volume (2 kcal per mL) to aid in fluid management. It is best to initiate tube feedings at a slow rate in this population and advance the feeding rate gradually to prevent osmotic diarrhea. Because patients on CRRT demonstrate improved clearance of nitrogenous wastes, fluid, and electrolytes, standard enteral formulas may be used. In this case, selection likely depends more on accompanying clinical conditions than on renal status. For example, a low-carbohydrate formula may be more appropriate for the CRRT patient with glucose intolerance than the typical calorically dense renal formulas.

Delayed gastric emptying related to dialysis treatment, diabetes, high blood urea nitrogen levels, hyperglycemia, or postoperative gastrointestinal complications can lead to enteral feeding intolerance in patients with renal failure. PN is indicated when the enteral route cannot safely be used to fully meet daily nutritional requirements. In general, standard amino acid solutions can be used. When fluid volume restriction is necessary, concentrated 15% amino acids solutions are helpful. A parenteral amino acid solution of equal amounts of essential amino acids and standard amino acids at a dose of 1 g per kg

TABLE 192.2

SPECIALTY ENTERAL PRODUCTS FOR USE IN RENAL FAILURE

Manufacturer	Product	Caloric density (kcal/mL)	NPC:N	Protein (g/L)	Carbohydrate of total kcal (%)	Fat of total kcal (%)	PO_4 (mg/L)	K (mg/L)	Na (mg/L)
Nestle[a]	Renalcal	2.0	338:1	34.4	58	35	—	—	—
Nestle[a]	NutriRenal	2.0	143:1	70	40	46	700	1,256	740
Abbott[b]	Nepro	2.0	154:1	70	43	43	685	1,060	845
Abbott[b]	Suplena	2.0	393:1	30	51	43	730	1,120	790
Nestle[a]	Novasource Renal	2.0	140:1	74	40	45	650	810 or 1,100[c]	1,000 or 1,600[c]

[a]Nestle Healthcare Nutrition (Minnetonka, MN).
[b]Abbott Nutrition (Columbus, OH).
K, potassium; Na, sodium; NPC:N, nonprotein calorie to nitrogen ratio; PO_4, phosphorus; —, negligible amounts.

per day may be given in cases of severe intolerance to standard mixtures despite intensive dialysis. Patients receiving enteral or parenteral preparations using essential amino acids as the sole source of nitrogen have demonstrated conflicting results concerning improvement in nitrogen balance and overall recovery of renal function [14,28,29]. Also, nonessential amino acids may become conditionally essential for protein synthesis and ammonia detoxification when the patient is under the stress of certain disease states. Thus, the use of formulations containing only essential amino acids should be reserved for less than 2 weeks of treatment in quantities less than 0.5 g per kg per day for patients with worsening renal function who are unable to begin dialysis.

Intradialytic parenteral nutrition (IDPN) is another means of nutritional support designed for use in malnourished HD patients unable to meet full protein and energy requirements by the oral or enteral route. IDPN may offer some advantages over PN in that dedicated vascular access is not needed and administration is done during dialysis therapy to avoid fluid overload. On the other hand, IDPN alone cannot provide adequate daily nutrition; it places the patient at high risk for hyperglycemia with insulin resistance, and expenses of the treatment are comparable to PN [30]. Several trials have attempted to demonstrate the efficacy of IDPN with favorable results; however, limitations in study design have left health care professionals wary of supporting its use in clinical practice [31]. A recent prospective study of 16 malnourished HD patients receiving IDPN revealed a significant weight gain after 6 months of IDPN treatment [32]. No control group was used in this study and no other outcome variables (i.e., morbidity, mortality) were adequately evaluated. At present IDPN should not be used as a substitute for total PN, especially in the critical care setting.

Summary of Nutritional Recommendations

Primary efforts of the caregiver should be directed toward management of the various nutritional and metabolic disorders commonly associated with renal failure. Adequate nutrient provision may optimize renal function, improve nutritional status, and raise the chances of survival in ARF patients [33]. Protein and energy requirements are largely dependent on the underlying causes of renal failure in the critically ill patient. ARF secondary to sepsis or severe injuries places a far greater nutrient demand on patients than that of nephrotoxic drug-induced ARF. The Harris–Benedict equation is used to calculate basal energy requirements, which is then multiplied by an activity and stress factor to determine total energy expenditure. Estimates of total energy expenditure in a critically ill population are typically between 30 and 45 kcal per kg per day. Increasing energy above this does not improve nitrogen balance [34]. Patients with a prolonged stay in the ICU may benefit from the more accurate predictions of energy expenditure afforded by indirect calorimetry [35]. Nondialyzed patients with ARF require a protein restriction of less than 0.5 g per kg of essential amino acids or 0.6 to 1.0 g per kg per day of mixed protein sources. However, such severe restrictions should not be imposed for longer than 2 weeks, and importance should be given to adequate energy provision for protein sparing. Patients receiving intermittent HD require 1.2–1.5 g per kg per day of mixed protein sources, whereas those undergoing CRRT can tolerate protein levels of up to 2.5 g per kg per day. Serum electrolytes should be monitored daily with additives adjusted on an individual basis. Standard vitamins and trace minerals can safely be provided to renal failure patients in the ICU. Fluid allowances for nondialyzed or HD patients are based on 24-hour urine output with an additional 500 mL for insensible losses. Those undergoing CRRT should be permitted additional fluid for provision of full nutritional support. A summary of recommendations supported by randomized controlled trials is included in Table 192.3.

TABLE 192.3

NUTRITION SUPPORT IN ACUTE KIDNEY INJURY

Increasing energy intake from 30 to 40 kcal/kg/d does not improve nitrogen balance and results in elevated levels of triglycerides and blood sugars [34].
Protein intake of 2.5 g/kg/d is recommended to achieve positive nitrogen balance in patients on CRRT.
Indirect calorimetry can improve the accuracy of energy provision in patients on CRRT.

LIVER FAILURE

As the central regulatory organ of the body, the liver is responsible for the metabolism, storage, activation, transport, and synthesis of many vital nutrients. Biochemical reactions fundamental to carbohydrate metabolism such as glycogenesis and gluconeogenesis are carried out in the liver. Albumin, transferrin, prealbumin, and prothrombin are a few of the major serum proteins generated in the liver. Fatty acid oxidation as well as the production of bile salts, triglycerides, and cholesterol for lipid absorption and transport is part of the normal hepatic function. The liver is also responsible for the catabolism of various potentially toxic substances including ammonia, alcohol, and acetaminophen. Liver damage can lead to the disruption of many of these processes; however, due to the large capacity for hepatic reserve, dysfunction is not usually seen until 80% to 90% of the liver cells have been injured [36].

A number of insults can initiate the cellular degeneration of acute or chronic liver disease. Viral infection, alcohol use, medications or other hepatotoxic agents, cardiac shock, chronic cholestasis, metabolic disorders, and autoimmune diseases are all potential instigators of liver injury. The damage can be so sudden and severe that it results in fulminant hepatic failure (FHF), a rare disease involving extensive liver necrosis and often culminating in death. Complications of FHF include metabolic abnormalities such as hypoglycemia or acidosis, hemodynamic instability, cerebral edema, sepsis or immunosuppression, and the hepatorenal syndrome. The presence of hepatic encephalopathy (HE), manifested by several neurologic, behavioral, and neuromuscular changes, may be able to predict the prognosis of FHF depending on the severity of the impairment [37]. Treatment of FHF often involves nutritional intervention; however, no controlled studies have been done to assess the benefits of nutrition therapy in this population.

Patients with acute hepatitis tend to be highly catabolic in the setting of severe gastrointestinal distress. Nausea, vomiting, and anorexia with occasionally concurrent acute pancreatitis may preclude the ability for oral intake. Short-term nutrition support is often necessary until causes of the acute injury to the liver have been identified and treated.

The end stage of most chronic liver diseases is the development of cirrhosis. Cirrhosis is characterized by repeated episodes of necrosis, followed by regrowth and formation of connective scar tissue. The resulting disruption of normal hepatic structure increases resistance of blood flow to the liver. Portal hypertension, esophageal varices with gastrointestinal bleeding, and ascites often stem from altered hepatic circulation in cirrhotic patients. Clinical evidence of cirrhosis can progress from elevated serum transaminases and jaundice to

hypoalbuminemia and HE. Malnutrition has been documented in up to 100% of hospitalized patients with alcoholic liver cirrhosis [38]. It is important to note that the presence of esophageal varices or ascites does not preclude the use of small bowel nasoenteric tube feeding in malnourished cirrhotic patients [39]. Several controlled trials using enteral nutrition in this population have demonstrated improvements in liver function tests, nutritional status, nitrogen balance, length of hospitalization, and overall prognosis [40–42]. The achievement of positive nitrogen balance did not have a negative impact on encephalopathy, azotemia, edema, or ascites among the study groups.

Malnutrition and Metabolic Alterations

Malnutrition in acute and chronic liver disease is the result of a combination of factors. A decrease in oral intake is common in the patient with prolonged gastrointestinal distress, early satiety secondary to ascites, or excessive alcohol consumption. Maldigestion and malabsorption leading to steatorrhea is often seen with cholestasis or chronic pancreatitis. Malnutrition in liver failure is also closely linked to the presence of severe metabolic derangements characteristic of hypercatabolic states of organ injury. Impaired glycogen synthesis and storage as well as decreased hepatic degradation of stress hormones lead to the preferential use of lipid and protein reserves for gluconeogenesis [43]. Insulin resistance and glucose intolerance are usual complications of early liver failure. Hypoglycemia can occur in decompensated cirrhosis or FHF as a result of hepatic glycogen depletion and impaired gluconeogenesis.

Hepatic steatosis with concurrent depletion of adipose tissue stores is a frequent consequence of the imbalance between lipid uptake, fatty acid oxidation, and the release of lipoproteins by the damaged liver. It is important to note that hepatic steatosis is often preventable by avoiding overfeeding. Lipids are the primary source of energy in enteral nutrition supplements designed for use in liver failure patients. IV lipids are also metabolized well by critically ill patients with hepatic failure when given in amounts not to exceed the energy needs of the individual patient. A recent study by Druml et al. found no significant difference in uptake, hydrolysis, or oxidation of a 20% IV lipid emulsion in septic patients with hepatic failure versus in healthy controls [44].

Altered protein metabolism is by far the most challenging aspect of providing nutrition therapy to the critically ill patient with liver disease. Cirrhosis has long been established as a catabolic disease, with unremitting protein degradation and inadequate resynthesis leading to depletion of visceral protein stores and muscle wasting [45]. Under ordinary circumstances, the skeletal muscle collects circulating branched-chain amino acids (BCAAs) for the synthesis of glutamine and alanine, amino acids that are released into the bloodstream and taken up by the liver for use in hepatic gluconeogenesis. Glutamine is also a carrier for ammonia, a potentially toxic by-product of protein metabolism. Ammonia is normally converted into urea by the liver and excreted by the kidneys. As liver function declines, uptake of serum glutamine is diminished and the degradation of ammonia into urea is impaired. In this case, excess serum glutamine and ammonia is diverted to renal pathways for direct excretion by the kidneys.

Adequate protein intake is therefore essential in the liver patient not only for the provision of energy by gluconeogenesis but also for the preservation of skeletal muscle mass and the prevention of HE. The clinical practice of protein restriction in patients with liver damage is common, for fear of precipitating or worsening central nervous system changes associated with HE. Several protein-related theories have been proposed regarding the development of HE, although it is of significance that the occurrence of encephalopathy has not been observed to directly correlate with protein intake in cirrhotic patients [46]. IV protein solutions with higher concentrations of BCAAs have been developed for use in liver disease based on the following hypothesis. As the use of BCAAs by skeletal muscle increases, serum levels decrease, thereby leaving an imbalance of BCAAs and aromatic amino acids at the blood–brain barrier. With less opposition from BCAA, aromatic amino acids readily cross into the central nervous system to form "false neurotransmitters." The false neurotransmitters compete with actual neurotransmitters for binding sites and disrupt normal central nervous system function to cause symptoms of HE [47].

Elevated serum ammonia concentrations have also been implicated in the pathogenesis of HE. Ammonia metabolites such as glutamine in cerebrospinal fluid have been correlated with the severity of encephalopathy [48]. Plauth et al. evaluated differences in serum ammonia levels between enterally and parenterally fed cirrhotic patients' status post–transjugular intrahepatic portosystemic shunt placement [49]. The small intestinal metabolism of enterally fed glutamine was found to produce significantly greater serum ammonia levels than the direct systemic infusion of parenterally fed glutamine. This suggests that PN may allow for a safer way to provide protein to encephalopathic patients. Enteral or parenteral administration of glutamine, however, is not recommended in patients with moderate to severe liver disease [50].

Zinc plays an important role in the regulation of nitrogen metabolism and zinc deficiency has been implicated in the pathogenesis of hepatic encephalopathy. Zinc supplementation therefore would seem to be a potential target for therapy and many studies have tried to address this question with conflicting results. To date there is no clear evidence of a beneficial effect for zinc supplementation for patients with hepatic encephalopathy [51].

Enteral and Parenteral Formulations

As mentioned previously, enteral and parenteral formulas for use in liver failure are designed to normalize plasma amino acid concentrations and improve encephalopathic symptoms. Hepatic enteral nutrition products are generally calorically dense, enriched with BCAAs, and of low-to-moderate fat content (Table 192.4). IV solutions for use in hepatic failure consist of 8% amino acids with 36% of total amino acids provided as BCAA (e.g., valine, isoleucine, and leucine) and only 2% as aromatic amino acids (e.g., tryptophan, phenylalanine, and tyrosine). These include Aminosyn-HF (Hospira, Inc., Lake Forest, IL), Hepatasol (Clintec Nutrition, Deerfield, IL), and HepatAmine (B. Braun Medical, Inc., Irvine, CA). Several leaders of nutrition-related research have published studies, reviews, and meta-analyses on the topic of oral or enteral BCAAs and HE, although consensus is still lacking among them [52–54]. Differences in the degree of encephalopathy, duration of treatment, type of control therapy, and amount of BCAAs supplied have limited the ability to draw distinct conclusions. Numerous research trials have also been conducted in an attempt to demonstrate clinical benefits of BCAA-enriched PN. A meta-analysis of seven such trials concluded that encephalopathy and survival rates were significantly improved among patients treated with BCAAs versus the control groups treated mainly with large doses of dextrose and lactulose or neomycin [55]. It should be noted, however, that improvement in encephalopathy did not always correlate with changes in serum amino acid levels. Other factors may have influenced mental status and mortality in these patients. A Cochrane Review from 2003 looked at 11 randomized trials (556 patients) regarding the effect of BCAA on hepatic encephalopathy [56]. Compared to the control regimens, the BCAA arms showed improvement

TABLE 192.4

SPECIALTY ENTERAL PRODUCTS FOR USE IN HEPATIC FAILURE

Manufacturer	Product	Caloric density (kcal/mL)	NPC:N	Protein (g/L)	BCAA of total protein (%)	Carbohydrate of total kcal (%)	Fat of total kcal (%)	MCT of total fat (%)	PO_4 (mg/L)	Na (mg/L)
Nestle[a]	NutriHep	1.5	209:1	40	50	77	12	66	1,000	320
Hormel[b]	Hepatic-Aid II	1.2	148:1	44.1	46	57	28	0	0	<585

[a]Nestle Healthcare Nutrition (Minnetonka, MN).
[b]Hormel Health Labs, Inc. (Savannah, GA).
BCAA, branched-chain amino acids; MCT, medium-chain triglyceride; Na, sodium; NPC:N, nonprotein calorie to nitrogen ratio; PO_4, phosphorus.

in encephalopathy at the end of the treatment. There was no effect on survival. Given the lack of follow-up, poor quality, and the small sample size of these studies, however, the reviewers concluded that there is no convincing evidence that BCAA have a beneficial effect on patients with hepatic encephalopathy [57]. In one large, randomized trial by Muto et al, oral BCAA given to patients with cirrhosis improved the combined rate of death and progression to liver failure [56]. Iwasa et al. showed improvement in regional cerebral blood flow in patients with cirrhosis treated with BCAA [58]. In regards to PN, few published studies exist to date comparing BCAA-enriched TPN to parenteral solutions containing standard amino acids [59–61]. No differences in outcome were noted in each of these studies.

Nevertheless, recommendations for clinical practice may be made from the evidence at hand. A primary focus in the management of HE should be on treatment of the underlying causes [9]. Dehydration, infection, electrolyte abnormalities, gastrointestinal bleeding, acid–base imbalances, and medications have been implicated in the occurrence of encephalopathy among critical care patients. In most acute cases, mental status improves with correction of precipitating abnormalities. Use of lactulose or neomycin, or both, for bowel cleansing and sterilization is the first line of treatment for hyperammonemia. The practice of restricting dietary protein in cirrhotic patients, especially those with HE, may seem prudent given the clear relationship between serum ammonia levels and poor outcomes. However, Cordoba et al. showed in a randomized controlled trial that restricting protein intake during encephalopathy had no beneficial effect [62]. When nutrition support is needed, a standard protein formula can be initiated at doses of 0.6 to 0.8 g per kg per day [63]. Restriction of protein is only necessary until the causes of encephalopathy have been identified and treated. To maintain nitrogen balance, nutrition support should be advanced as tolerated to goals of 1.0 to 1.5 g per kg per day in critical care situations [64]. BCAA-enriched formulas are solely reserved for use in severe encephalopathy refractory to standard treatment, but evidence for their role as a first choice is mounting.

Nutrition Assessment

Traditional parameters of nutritional status such as weight loss and depletion of visceral protein stores are frequently masked among liver failure patients by the presence of ascites or edema. Serum albumin, prealbumin, and transferrin levels are more reflective of disease-related intravascular volume expansion and increased protein catabolic rate than the severity of nutritional deficit. Despite this, albumin remains an important marker of PCM among liver patients. Because the upper extremities tend to escape the fluid retention often seen in liver patients, mid-arm muscle circumference and triceps skinfold measurements are considered to be the most accurate tools for nutrition assessment in this population. Recent investigations have centered on the detection of those nutritional parameters most predictive of survival, indicative of PCM, and responsive to treatment in liver failure patients. A prospective study of 271 mildly to severely malnourished patients with chronic alcoholic hepatitis revealed significant improvements in visceral proteins and mid-arm muscle mass in response to intensive nutrition therapy along with oral administration of oxandrolone, an androgenic anabolic steroid [46]. Severe reduction in mid-arm muscle circumference and triceps skinfold measurement, suggestive of muscle mass and body fat depletion were found to be independent predictors of survival in a study of 212 hospitalized cirrhotic patients. In this study, Alberino et al. also advised the inclusion of upper-arm anthropometry to improve prognostic accuracy of the Child-Pugh score, a commonly used classification of the severity of liver disease [65]. A comprehensive analysis of all available data, including physical examination, anthropometric measurements, and laboratory values, may therefore be the best determinant of nutritional status in liver disease.

Summary of Nutritional Recommendations

In devising a plan for nutritional management of the critically ill patient with liver disease, one must consider the etiology of the disease, associated complications and metabolic abnormalities, and concurrent disease processes (Table 192.5). Despite the inherent difficulties in obtaining an accurate dry weight, the Harris-Benedict equation with stress factors may be used in most liver patients to estimate basal energy expenditure. Requirements for most patients are met with 25 to 35 kcal per kg per day or basal energy expenditure times 1.2 to 1.4, and standard protein doses of 1.0 to 1.5 g per kg per day [66]. Nonprotein calories are generally supplied in proportions of 50% to 70% carbohydrate and 30% to 50% fat in the setting of glucose intolerance. Patients demonstrating symptoms of persistent encephalopathy despite aggressive medical management require a temporary protein restriction of 0.6 to 0.8 g per kg per day pending treatment of underlying causes. If the patient does not respond to protein restriction, a BCAA-enriched formula should be used to promote nitrogen balance. Sodium and fluid restriction are indicated with ascites or edema. Recommended daily allowances of vitamins, minerals, and trace elements are usually sufficient in this population, although additional supplementation of thiamine and folate is customary in alcoholic cirrhosis. Pescovitz et al. document an elevated rate of profound zinc deficiency among patients with end-stage liver disease [67]. Supplementation of zinc in these cases may improve HE; however, efficacy of zinc as a routine therapy for encephalopathy is still controversial [68].

In the case of severe liver disease such as FHF, indirect calorimetry is a more accurate method of determining energy

TABLE 192.5

NUTRIENT REQUIREMENTS IN VARIOUS STAGES OF LIVER DISEASE

Degree of liver injury	Total energy (kcal/kg/d)	Protein or amino acids (g/kg/d)
Compensated cirrhosis	25–35	1.0–1.2 for maintenance, 1.2–1.5 for repletion
Decompensated cirrhosis	25–35	Begin with 0.6–0.8 of standard protein If improvement, advance to 1.2–1.5 as tolerated If refractory, supplement with BCAA until positive nitrogen balance is achieved
Fulminant hepatic failure	35–40	0.6–0.8, if improvement advance
Post–liver transplant	25–35	1.2–1.5

BCAA, branched-chain amino acids.
Data compiled from references [8,34,48,56,59,62].

requirements. Because patients in FHF have limited gluconeogenesis capacity, nutrition support should be initiated peripherally with 10% dextrose to limit the possibility of hypoglycemia and limit catabolism. To provide more substantial dextrose concentrations parenterally, central access is required. Fluid restriction is often necessary to prevent exacerbation of cerebral edema. However, with the use of peripheral 10% dextrose solution, large volumes are required to achieve nutritional goals. Protein administration should begin with 0.6 to 0.8 g per kg per day of a standard amino acid solution. Standard protein provisions should be advanced as tolerated to 1.2 to 1.5 g per kg per day if the encephalopathy improves. If the patient remains in negative nitrogen balance with severe encephalopathy, BCAA formulas should be used and advanced as tolerated to achieve positive nitrogen balance. Protein requirements in FHF are 1.5 to 1.75 grams per kg per day, and basal energy requirements in FHF are 35 to 40 kcal per kg per day provided as a mixture of carbohydrate and lipid substrates. A summary of recommendations supported by randomized controlled trials is included in Table 192.6.

TABLE 192.6

NUTRITION SUPPORT IN LIVER DISEASE: SUMMARY OF CONTROLLED TRIALS

Cirrhosis and severe malnutrition:

Total enteral tube feeding, compared to a regular diet, improves liver function and reduces mortality in hospitalized patients [40].

Alcoholic liver disease:

Protein calorie malnutrition correlates significantly with mortality, clinical severity of the liver disease, and biochemical liver dysfunction [42].

Supplemental enteral tube feeding, in addition to an oral diet, results in more rapid improvement of liver function in hospitalized patients [102].

Hepatic encephalopathy (acute):

Branched-chain amino acid enriched nutrition support leads to a more rapid resolution of hepatic encephalopathy, but has no affect on mortality [56].

Normal protein intake is well tolerated and results in less protein breakdown when compared to low protein intakes [62].

Note: Studies did not specifically focus on patients in the critical care setting and most were small in size.

Liver Transplantation

Currently, the best therapy for unsalvageable liver failure is liver transplantation [50]. It is important to note that not only must the nutritional status of the liver transplant recipient be considered, but also that of the donor. There is evidence to suggest that infusion of large quantities of dextrose can restore glycogen stores, that feeding the donor patient improves protein synthesis, that fish oils may increase hepatic energy content, and that glutamine offers some graft protection in ischemia-and-reperfusion injury [69,70].

Liver transplant candidates should undergo a comprehensive nutritional assessment to uncover signs of poor nutritional status. Once moderate-to-severe PCM has been established, nutrition support should be initiated to promote improved postoperative outcomes [50,71]. Nutrition support is also of value in the immediate posttransplant period. Hasse et al. randomized 50 posttransplant patients to receive standard enteral nutrition or parenteral electrolyte solutions until oral diets were tolerated [72]. A decreased incidence of infection and faster recovery of nitrogen balance was found in the enterally fed group during the first 21 days after undergoing orthotopic liver transplantation. Posttransplant patients are often faced with impaired glucose tolerance and hyperlipidemia, although standard lipid infusion is generally well tolerated and necessary to maintain glycemic control in this population. Tight blood glucose control with special emphasis on the increased risk for hypoglycemia may help reduce the chances for postoperative septic complications. Energy requirements are estimated using the Harris-Benedict equation multiplied by stress factors of 1.2 to 1.3, with protein needs estimated at 1.2 g per kg per day. No specific advantages have been found with regard to the use of BCAA-enriched amino acids solutions or fat emulsions containing medium- and long-chain triglycerides in this population [72].

PULMONARY FAILURE

Optimal functioning of the pulmonary system is essential to the maintenance of adequate nutritional status. Through the process of gas exchange, the lungs and supporting respiratory structures provide oxygen to vital tissues for nutrient metabolism. The respiratory system also plays a major role in regulation of acid–base balance. Pulmonary injury or insufficiency can lead to malnutrition and dependence on mechanical ventilation in the critically ill patient. Acute respiratory distress syndrome (ARDS), characterized by severe progressive

hypoxemia and mechanical ventilation, is a frequent result of trauma, sepsis, or surgery in the critical care setting. The patient with chronic obstructive pulmonary disease (COPD) may also undergo periods of acute exacerbation requiring intensive care. Malnutrition has been documented in up to 60% of this population, with the highest incidence occurring in the mechanically ventilated. In a 1996 study by Vitacca et al., nutritional prognostic indicators such as weight loss and percentage of ideal body weight were able to significantly predict the need for mechanical ventilation among hospitalized COPD patients. Decreased survival rates have been observed in malnourished, critically ill COPD patients as well [73,74].

Malnutrition may result from a variety of factors inherent to the pulmonary disease process. Hyperinflation of the lung with an associated decrease in abdominal volume often leads to anorexia, early satiety, and tube feed intolerance. Oral intake may also be hindered by dyspnea and fatigue during meal times. Significant weight loss is found in 20% to 40% of patients with forced expiratory volume in 1 second (FEV_1) of less than 50% [75]. Energy expenditure is reported to be up to 20% above normal in COPD due to the increased work of breathing [76]. Patients with significant COPD spend 430 to 720 kcal per day in the task of breathing, whereas normal subjects use only 36 to 72 kcal per day toward the same goal [9]. Impaired gas exchange with inadequate delivery of oxygen to body tissues has been implicated as a cause of malnutrition in COPD [77]. Increased levels of tumor necrosis factor, an inflammatory mediator, may additionally lead to alterations in energy expenditure and the development of anorexia in this population [78].

Effects of Malnutrition on Pulmonary Function

Just as pulmonary disease influences the onset of malnutrition, poor nutritional status may significantly impair several structural and functional components of the respiratory system [79]. Respiratory muscles display reduced efficiency and endurance during nutrition deprivation due to loss of muscle mass and depletion of energy reserves. Impaired respiratory muscle function eventually results in decreased ventilatory drive and inefficient gas exchange or hypercapnia and hypoxemia. Severe hypophosphatemia, often seen during rapid refeeding of malnourished patients, also adversely affects respiratory muscle function resulting in decreased delivery of oxygen to the tissues [80]. Hypoalbuminemia, associated with critical illness and malnutrition, decreases osmotic pressure, leading to the expansion of extracellular fluid and increased interstitial lung fluid or pulmonary edema. A reduction in pulmonary functional reserve capacity accompanies fluid retention in the lungs [81]. Immunity from respiratory tract infection relies heavily on the preserved integrity of the pulmonary system. Nosocomial pneumonia is the most common fatal infection among hospitalized individuals. Malnutrition in the setting of critical illness not only impairs immune response but also damages specific pulmonary defense mechanisms. Decreased secretion of immunoglobulin A, reduced alveolar macrophage recruitment, increased bacterial adherence to respiratory epithelium, and a weakened lung matrix are all potential outcomes of malnutrition leading to increased risk of pneumonia and mortality in the critically ill patient [9].

Nutritional Assessment

As previously mentioned, common indicators of nutritional status have correlated with the duration of mechanical ventilation and mortality in hospitalized COPD patients. Several recent studies have focused on uncovering specific parameters most predictive of nutritional status and outcome in this population. A large-scale, prospective study conducted by Landbo et al. observed strong associations between low body mass index (BMI) and increased mortality in subjects with severe COPD [82]. In a similar study, Hallin et al. demonstrated that patients who were under weight (BMI < 20) had a lower FEV_1 and a higher risk of dying within the next 2 years following their hospital admission [83]. It is unclear, however, if nutritional support in the chronic COPD patient can improve these outcomes.

In regard to defining nutritional status, Faisy et al. compared changes in bioelectrical impedance analysis with various anthropometric and biologic parameters among ICU patients with COPD and acute respiratory failure [84]. Bioelectrical impedance analysis more accurately detected severe alterations in nutritional status in those patients requiring mechanical ventilation, whereas anthropometric data were inconclusive. Low serum albumin levels were also significantly associated with increased mortality among patients in this study. Weight changes, serum albumin levels, and bioelectrical impedance analysis, if available, are thus used as valuable tools in assessment of nutritional status and prediction of outcome in patients with severe respiratory insufficiency.

An accurate measure of energy expenditure is of utmost importance in the nutritional care of the patient with pulmonary disease. Underfeeding, with the consequence of malnutrition, may increase risk of infection, prolong ventilator dependence, delay wound healing, and increase overall hospital morbidity and mortality. An overestimation of energy needs is associated with several metabolic, hepatic, and respiratory complications, including increased carbon dioxide production with inability to wean from mechanical ventilation (Table 192.7). McClave et al. demonstrated an inverse correlation between the degree of feeding in mechanically ventilated adults and the amount of air inspired and expired over the period of 1 minute [85]. Patients receiving greater than 100% up to 300% of nutritional needs as estimated by indirect calorimetry showed significant decreases

TABLE 192.7

POTENTIAL COMPLICATIONS OF OVERFEEDING

System	Complications
Metabolic	Hypermetabolism Hyperglycemia Increased lipogenesis Fluid overload Hypophosphatemia Hypokalemia Hypomagnesemia
Hepatic	Hepatic steatosis Cholestatic liver disease Elevated serum transaminases
Respiratory	Increased carbon dioxide production Hypercapnia Increased minute ventilation Increased ventilatory drive Decreased oxygen saturation Increased respiratory quotient Weakened respiratory muscles Difficulty weaning from mechanical ventilation

Data compiled from references [8,56,70,77,79,83,94,95].

in minute ventilation, whereas those receiving less than 100% of their caloric requirements had significant increases in minute ventilation. Ventilatory settings may be adjusted to account for minor discrepancies in provision of nutrient requirements without much setback; however, this study also revealed that only approximately 25% of hospitalized patients actually receive calories within 10% of energy requirements [86,87].

Indirect calorimetry is a clinical tool by which measurements of respiratory gas exchange are used to determine energy requirements and substrate utilization for a given subject. It continues to be the gold standard for establishing nutritional goals. Several researchers have examined the benefits of using indirect calorimetry over predictive equations to assess energy expenditure in critically ill patients with acute respiratory failure [85,87,88]. Flancbaum et al. found poor correlation between various predictive formulas and indirect calorimetry measurements. A 1997 review by Brandi et al. concluded that although several sources of error exist, indirect calorimetry remains the most appropriate measure of energy expenditure in mechanically ventilated patients. Recommendations were also made to obtain several measurements throughout the course of a patient's illness to more closely approximate nutritional requirements under fluctuating metabolic states. In cases in which indirect calorimetry is not available or not feasible, the Harris-Benedict equation may be used to estimate resting energy expenditure (REE), which is then multiplied by a stress factor of 1.3 to 1.5 to approximate energy requirements in this population.

Nutrient Requirements and Nutrient Impact on Pulmonary Function

Substrate utilization as assessed by indirect calorimetry is the ratio of oxygen consumed to carbon dioxide produced on metabolism of various macronutrients. This ratio is referred to as the respiratory quotient (R/Q). The oxidation of fat, protein, and carbohydrate produces an R/Q of 0.7, 0.8, and 1.0, respectively. Ideally, the R/Q of a given patient should approximate 0.85 to reflect metabolism of mixed substrates. When carbohydrate or total calorie provisions exceed energy requirements, R/Q levels rise above 1.0 to suggest fat synthesis. An R/Q of less than 0.7 is indicative of inadequate nutrition support with breakdown of bodily fat and protein stores. This information is useful for the adjustment of fuel mixtures within the nutrient prescription to avoid potentially harmful effects of over or underfeeding the ventilator-dependent patient.

The provision of carbohydrate in excess of 5 mg per kg per minute in severely stressed patients increases carbon dioxide production ($\dot{V}CO_2$) and may delay weaning from mechanical ventilation. Jih et al. reported the case of a septic ARDS patient who developed increased respiratory distress and hypercapnic acidosis in response to hypercaloric carbohydrate infusion [89]. Hypercapnia resolved as carbohydrate and total calories were decreased to levels consistent with indirect calorimetry measurements of REE. Talpers et al. maintain that total caloric intake has more of an impact on respiratory function in mechanically ventilated patients than excessive carbohydrate calories [90]. No difference in ($\dot{V}CO_2$) was observed upon variation in carbohydrate provisions with consistent total caloric intake (1.3 × REE). In contrast, increasing total caloric provisions (1.5 to 2.0 × REE) with fixed carbohydrate content led to a significant progressive increase in ($\dot{V}CO_2$). Administration of PN at a calorie level equal to indirect calorimetry measurements did not increase ($\dot{V}CO_2$) or ventilatory demand in a 1994 analysis of mechanically ventilated patients by Kiiski and Takala [91]. In many cases, sustained hyperglycemia in the critically ill mechanically ventilated patient signifies a need for decrease in carbohydrate or total calorie provisions rather than an incremental increase in insulin dosage.

The substitution of fat for carbohydrate calories may lower R/Q and decrease ($\dot{V}CO_2$) to ease weaning from the ventilator [92]. The use of IV fat emulsions (IVFE) is not without its drawbacks, however. Rapid infusion of IVFE may adversely affect gas exchange by decreased rate of clearance, deposition of lipid particles within the reticuloendothelial system, and subsequent reduction in pulmonary diffusion capacity. This effect is most often seen in patients with existing pulmonary dysfunction and with rates of lipid administration more than 1 kcal per kg per hour [93]. Immune function is also compromised by rapid infusion of IVFE in patients with pulmonary insufficiency. Specific omega-6 polyunsaturated fatty acids, including linoleic acid, serve as precursors for synthesis of vasoconstrictive prostaglandins and proinflammatory eicosanoids. The resulting activation of pulmonary neutrophils limits bacterial clearance from systemic circulation and increases uptake of bacteria into the lungs [94]. Inflammatory cells, possibly activated by lipids, release phospholipase A[2] and platelet-activating factor, enhancing edema formation, inflammation, and surfactant alterations [95]. Specialized enteral formulas designed to decrease production of proinflammatory agents and enhance immune function in pulmonary patients are discussed in the following section.

Battistella et al. examined the effects of withholding IVFE for 10 days in 57 polytrauma patients requiring total PN [96]. Results indicated a significantly greater length of ICU and hospital stay, longer duration of mechanical ventilation, and higher incidence of infection in patients receiving IVFE. It is, however, impossible to fully assign the differences to the withholding of lipids, as this group did not receive extra calories to account for the absence of lipid. The group with IVFE received 25% more total calories, which could have contributed to the increase in adverse outcomes in this group of patients. Clinical experience has shown that IVFE may be given safely in the range of 20% to 40% of nonprotein calories infused over a period of 12 to 24 hours in the critically ill patient [9].

Protein requirements in critically ill patients with pulmonary failure are elevated in accordance with the hypercatabolism of stressed states. Consequences of protein malnutrition, including loss of diaphragmatic muscle mass, are significant enough to warrant 1.5 to 2.0 g per kg per day of protein depending on the need for repletion [97]. Unfortunately, an increase in ventilatory drive and minute ventilation may be seen with protein infusion. BCAA formulas, in particular, may result in severe respiratory distress [98]. It is therefore recommended that protein provisions be advanced slowly with close attention to respiratory function in mechanically ventilated patients.

Enteral and Parenteral Nutrition

The use of enteral nutrition or PN is necessary in nearly every patient that requires prolonged ventilator support. However, the use of PN in the patient with pulmonary failure has become increasingly scrutinized. Plurad et al. showed that the administration of PN was independently associated with late onset ARDS [99]. In general, parenteral nutrition should be avoided in this patient population. In those patients in whom PN must be used secondary to inability to use the gastrointestinal tract, there is new evidence to suggest that omega-3 fatty acids-supplemented parenteral nutrition may be better than standard formulas [100]. Currently, these formulas are not available in the United States.

Although the intubated and sedated patient is at increased risk of aspiration, enteral nutrition is clearly the preferred route of feeding due to improved outcomes, lower costs, decreased

TABLE 192.8

SPECIALTY ENTERAL PRODUCTS FOR USE IN PULMONARY FAILURE

Manufacturer	Product	Caloric density (kcal/mL)	NPC:N	Protein (g/L)	Carbohydrate of total kcal (%)	Fat of total kcal (%)	MCT of total fat (%)	PO_4 (mg/L)	Na (mg/L)
Nestle[a]	Nutrivent	1.5	114:1	67.5	27	55	40	1,200	1,170
Abbott[b]	Pulmocare	1.5	125:1	62.6	28	55	20	1,060	1,310
Abbott[b]	Oxepa	1.5	125:1	62.5	28	55	N/A	1,060	1,310
Nestle[a]	Novasource Pulmonary	1.5	102:1	75	40	40	N/A	1,070	1,290
Nestle[a]	Respalor	1.5	102:1	75	40	40	N/A	1,000	1,270

[a]Nestle Healthcare Nutrition (Minnetonka, MN).
[b]Abbott Nutrition (Columbus, OH).
MCT, medium-chain triglycerides; N/A, data not available; Na, sodium; NPC:N, nonprotein calorie to nitrogen ratio; PO_4, phosphorus.

risk of sepsis, and improved preservation of gut mucosal barrier. Proposed mechanisms by which risks for aspiration may be reduced include timely weaning of the patient off pressor support, maintenance of the patient in a semirecumbent body position, and the use of transpylorically placed feeding tubes [80,101]. Gastric feedings may work equally as well if gut motility is intact. Kearns et al. [102] found no clear difference between the use of small bowel and gastric feeding tubes in the prevention of ventilator-associated pneumonia [102]. Despite this, small bowel tube placement remains the preferred method of feeding for improved nutrient intake in a population frequently hindered by gastric ileus.

Standard enteral formulas may be used in most patients with pulmonary dysfunction, however, current recommendations advise that specialized nutritional support is indicated in the critically ill who are unable to consume an oral diet within 5 to 10 days [103]. Fluid and sodium-restricted tube feedings are often necessary until the risk for pulmonary edema resolves. Enteral products designed specifically for use in pulmonary disease should be reserved for patients with existing COPD and increasing difficulty weaning off the ventilator (Table 192.8). These formulas are typically nutrient dense with moderate to high levels of fat (40% to 60%). Akrabawi et al. examined the effects of a moderate fat (Respalor; 41% fat) (Novartis Nutrition, Minneapolis, MN) versus high fat (Pulmocare; 55% fat) (Abbott Nutrition, Columbus, OH) enteral formula on gastric emptying times and pulmonary function in 36 patients with COPD [104]. Although no differences were found in pulmonary function between the two feedings, gastric emptying times were significantly enhanced with the moderate-fat meal. This implies possible benefits, including improved tolerance and overall increased nutrient intake and absorption with the use of a moderate-fat enteral nutrition product providing 30% of total fat as medium-chain triglycerides.

A specialty enteral feeding was designed to counteract the inflammatory cascade and improve oxygenation in the patient with ARDS. This product (Oxepa, Abbott Nutrition, Columbus, OH) is supplemented with eicosapentaenoic acid and gamma-linolenic acid, two fatty acids with anti-inflammatory properties. Gadek et al. compared the effects of this specialized enteral formula (Oxepa) with a control feeding (Pulmocare) in 98 critically ill patients with ARDS [105]. The two formulas differed only in terms of lipid composition and increasing levels of antioxidants in the experimental product. Significant beneficial effects on oxygenation (partial arterial pressure of oxygen/fraction of inspired oxygen: 203 vs. 168), minute ventilation, duration of mechanical ventilation (11 vs. 16.3 days; $p = 0.011$), and length of ICU stay (12.8 vs. 17.5 days; $p = 0.016$) were demonstrated in patients fed the specialized diet compared with controls. Further studies are necessary to clearly identify the benefits of these specialized formulas, but based on the recommendations by several nutritional organizations, these formulas should be chosen in patients with ARDS [106,107].

Immunonutrition has also received substantial recent attention. Possible advantages include reduced duration of mechanical ventilation and decreased incidence of pulmonary infection among the critically ill. Atkinson et al. conducted a prospective, double-blind, controlled trial on the use of IMN Impact (Nestle, Minnetonka, MN), an enteral formula supplemented with arginine, purine nucleotides, and omega-3 fatty acids [108]. Three hundred and sixty-nine ICU patients were randomized to receive IMN Impact or an isocaloric, isonitrogenous enteral feed. There was no difference in hospital mortality rate between the two groups. Those patients receiving more than 2.5 L of IMN Impact within 72 hours of ICU admission ($n = 50$ IMN Impact vs. $n = 51$ control formula) had a significant reduction in median duration of mechanical ventilation (6.0 vs. 10.5 days; $p = 0.007$) and median length of hospital stay (15.5 vs. 20.0 days; $p = 0.03$). Mendez et al. found opposite effects when comparing an immune-enhancing formula (Perative, Abbott Nutrition, Columbus, OH) with an essentially isonitrogenous, isocaloric standard feeding [109]. Overall mortality was again identical between the two groups; however, those receiving immunonutrition remained longer on the ventilator (16.4 vs. 9.7 days) and in the hospital (32.9 vs. 22 days) than the control group. It is important to note that Perative does not contain purine nucleotides and delivers omega-3 fatty acids in the form of canola oil rather than fish oils. A recent review of 23 clinical trials involving immune-enhancing formulas concluded that immunonutrition has established a reduced need for ventilation and a decreased risk of infectious complications in malnourished postsurgical ICU patients with known COPD [110]. According to the most recently published guidelines, the use of specialized enteral formulas with anti-inflammatory profiles is now recommended in patients with ARDS with the potential to improve outcomes [107].

Summary of Nutritional Recommendations

Sustained nutrition therapy in mechanically ventilated patients has demonstrated several benefits including increased serum albumin, reduced anasarca, improved respiratory function, and facilitated weaning from the ventilator. Overfeeding can be highly detrimental to the ventilator-dependent critically ill

patient. However, it appears that more often than not, nutritional requirements for these patients are underestimated. Daily energy needs are best determined by indirect calorimetry; although, approximations may be made with predictive equations and stress factors of 1.3 to 1.5 × REE or 25 to 30 kcal per kg. Careful monitoring of intake and output, weight changes, and respiratory status is required when indirect calorimetry is not available. Protein needs generally range between 1.5 to 2.0 g per kg per day, with cautious advancement to goal levels. Carbohydrate dosages should not exceed 5 mg per kg per minute provided as 60% to 80% of nonprotein calories. A conservative dose of fat emulsion is recommended in the range of 20% to 40% of nonprotein calories infused over 12 to 24 hours. Enteral feedings with roughly 30% fat, 50% carbohydrate, and 20% protein are generally well tolerated, provided nutrient requirements are not exceeded. Modified and immune enhanced formulas are gaining favor, but should be reserved for those with ARDS and obvious difficulties weaning off the respirator. Maintenance of fluid balance is also of primary importance in the critically ill patient with pulmonary insufficiency. Concentrated parenteral solutions and enteral formulas should be used as necessary. Sodium restriction is indicated in patients with pulmonary edema or congestive heart failure. Hypophosphatemia may be avoided by gradual advancement of nutrition support in severely malnourished patients. Serum phosphorus, potassium, and magnesium levels should be monitored routinely and deficiencies should be corrected aggressively in the critically ill patient. A summary of recommendations supported by randomized controlled trials is included in Table 192–9.

TABLE 192.9

NUTRITION SUPPORT IN PULMONARY DISEASE

Early enteral nutrition (within 24–48 h admission) decreases infectious complications, including pneumonia.
Enteral formulas with anti-inflammatory lipid profiles and antioxidants improve oxygenation, decrease duration of mechanical ventilation, and shorter intensive care unit length of stay in acute respiratory distress syndrome or acute lung injury [105].
Enteral formulas that provide immunonutrition (arginine, glutamine, nucleic acids, omega-3 fatty acids, antioxidants) decrease duration of mechanical ventilation, organ failure, hospital and intensive care length of stay, and mortality [108, 111].

Note: Early enteral nutrition is not a part of this chapter but a general concept that has been indirectly related to decrease pneumonia.

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SECTION XVI ■ RHEUMATOLOGIC, IMMUNOLOGIC, AND DERMATOLOGIC PROBLEMS IN THE INTENSIVE CARE UNIT

NANCY Y.N. LIU

CHAPTER 193 ■ RHEUMATOLOGIC DISEASES IN THE INTENSIVE CARE UNIT

NANCY Y.N. LIU AND JUDITH A. STEBULIS

Patients with established rheumatologic diseases are rarely admitted to the intensive care unit (ICU) because of their inflammatory joint disease. However, since many of these diseases include systemic involvement, organ system failure and complications of therapy are common reasons for ICU admission. Other musculoskeletal problems frequently encountered in the intensive care setting include (a) patients whose underlying rheumatic diseases may pose certain problems in the planning and execution of certain critical care procedures, such as endotracheal intubation or (b) patients in whom acute rheumatic syndromes develop during their hospitalization.

ACUTE RHEUMATIC DISEASES IN THE INTENSIVE CARE SETTING

Several acute musculoskeletal disorders occur with increasing frequency in selected populations of hospitalized patients, including those in the ICU. The most common is crystal-induced arthritis due to monosodium urate, calcium pyrophosphate dihydrate, basic calcium phosphate (BCP)-hydroxyapatite, or calcium oxalate crystals. Two other acute arthritides include septic arthritis from bacteremia and spontaneous hemarthrosis due to complications from anticoagulation therapy or bleeding diathesis.

Gout

Pathogenesis

Gout is characterized by initial intermittent attacks of mono- or polyarticular arthritis in the setting of prolonged hyperuricemia. Over many years, attacks become more frequent and chronic arthropathy may develop. Acute gout is triggered by precipitation or shedding of monosodium urate crystals in the joint space or nearby soft tissues, provoking an intense inflammatory reaction. Regardless of a primary or secondary etiology of hyperuricemia, marked fluctuations in serum urate levels increase the risk of acute gout.

Although the specific triggering event that initiates an isolated attack may be difficult to define, many factors produce serum urate fluctuations and result in an increased incidence of secondary gout in ICU patients. A reduction in glomerular filtration rate from either intrinsic renal disease or decreased effective arteriolar blood volume will result in reduced filtered load of urate, hyperuricemia, and an increased risk of gout. In addition, a reduction in effective arteriolar blood volume results in enhanced tubular reabsorption of urate. Since organic acids such as lactic acid, β-hydroxybutyric acid, and acetoacetic acid may competitively inhibit the renal tubular secretion of uric acid, conditions in which these acids accumulate will also lead to hyperuricemia. Mechanisms of hyperlacticacidemia in the critically ill patient are multiple.

Drug-induced hyperuricemia is a common cause of gout in both hospitalized and nonhospitalized patients. Diuretic therapy decreases effective arteriolar blood volume and also may directly inhibit renal tubular secretion of uric acid. Although thiazide diuretics are the most commonly implicated cause of hyperuricemia and gout, other diuretics including furosemide, acetazolamide, ethacrynic acid, and diazoxide are also potential culprits. Furosemide and diazoxide may also induce hyperlacticacidemia.

In addition to diuretics, other drugs associated with hyperuricemia include low-dose salicylates (less than 2.0 g per day), pyrazinamide, levodopa, α-methyldopa, and cyclosporine. Because of the uricosuric effect of radiocontrast media, a contrast study might precipitate an attack of acute gout. Finally, a hyperuricemic patient who undergoes any surgical procedure is at risk for postoperative gout.

Clinical Features

Gout is easily identifiable and treatable. Classically, the patient with acute gout complains of sudden onset of an exquisitely painful joint that involves one or more sites in an asymmetric pattern. The attack is sometimes accompanied by low-grade fever, particularly in a polyarticular presentation. The great toe is involved in more than 50% of the initial acute attacks and in 90% of acute attacks at some time in the course of the disease. Other common sites of involvement in order of observed frequency include insteps, ankles, knees, wrists, fingers, and elbows. Periarticular sites of urate deposition in bursae, tendons, and soft tissues may be similarly inflamed during an acute attack. On examination, the involved area is erythematous, swollen, warm, and exquisitely painful on palpation, and sometimes with joint motion. The overlying erythema and edema often extends beyond the joint capsule and can mimic cellulitis or bursitis. The presence of lymphangitis or lymphadenopathy and the absence of pain on joint motion are more consistent with cellulitis. Bursitis can be distinguished from true arthritis since full joint extension is preserved in bursitis, and the region of erythema is not within the borders of the joint compartment. If clinical suspicion of joint infection is low then diagnostic arthrocentesis should be avoided until a therapeutic trial of appropriate antibiotics for cellulitis has been completed. Otherwise, there may be a risk of introducing organisms into a sterile joint. However, if motion is restricted or if radiography suggests an effusion, a diagnostic arthrocentesis should be performed before the institution of any therapy.

The diagnosis of gout is confirmed when aspirated synovial fluid or soft tissue site reveals negatively birefringent monosodium urate crystals within polymorphonuclear neutrophils (PMNs) under polarizing light microscopy. Gouty synovial fluid is inflammatory, with more than 2,000 leukocytes

per μL, occasionally as high as 100,000 per μL, and PMNs predominate in the cell differential. Since gout and septic arthritis have similar clinical features and rarely coexist, aspirated synovial fluid should always be Gram stained for microorganisms and cultured. Elevations in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and peripheral leukocytosis cannot distinguish gout from other inflammatory states. Serum urate may be normal during an acute attack, while an elevated level does not confirm the diagnosis without crystal identification.

Therapy

Once the diagnosis of acute gout is established, the immediate aim of therapy is to terminate the attack by interruption of the inflammatory response. Long-term management (e.g., prevention of recurrent attacks, sequelae of tophaceous disease or renal stones) need not be considered in the ICU setting. In fact, the initiation or discontinuation of any drugs that alter urate levels (i.e., allopurinol, febuxostat, probenecid, or salicylates) may prolong the acute attack. Asymptomatic hyperuricemia should not be treated.

Corticosteroids. Systemic and intra-articular steroids are effective for the treatment of gout. Intravenous (IV) methylprednisolone (100 to 150 mg IV daily for 1 to 3 days) or intramuscular triamcinolone acetonide (60 to 80 mg daily for 1 to 3 days) is the preferred agent in critically ill patients [1]. Oral prednisone may also be effective in doses of 20 to 30 mg twice per day initially and tapered over 7 to 14 days with decrements of 10 mg every two days [1]. Potential complications of steroid treatment include hyperglycemia, fluid retention secondary to mineralocorticoid effects, and hypothalamic-pituitary-adrenal suppression. Intra-articular corticosteroid injections are an excellent choice for acute gouty arthritis if few joints are involved since systemic side effects are avoided. Steroid injections provide rapid resolution of symptoms, usually within 12 to 24 hours, but if infection is suspected, corticosteroid injection should be delayed until culture results are available. Intra-articular corticosteroids are quite effective in small joints if performed by physicians skilled in these injections. Dosing ranges from 10 to 60 mg methylprednisolone or equivalent triamcinolone, depending on the size of the joint involved.

Adrenocorticotropic Hormone. Adrenocorticotropic hormone (ACTH) has been used for more than 40 years for the treatment of gout. Dosing regimens vary, starting at 40 to 80 IU intramuscularly, subcutaneously, or intravenously 1 to 3 times a day until symptoms abate. Adverse effects include mild hyperglycemia and fluid overload. Although the overall safety profile and efficacy of ACTH are excellent, its use is limited by its lack of availability and prohibitive cost. Its anti-inflammatory effects are result of interruptions of microtubule function in multiple cell types but particularly PMNs' function in chemotaxis, adhesion, phagocytosis, and production of cytokines.

Colchicine. Colchicine is one of the established treatments for gout. Its main mechanism of action involves formation of a reversible complex with the tubulin subunit of microtubules leading to reduced activation and migration of PMNs. Oral colchicine is absorbed in the small intestine and excreted in the bile and urine, reaching a peak serum level in 2 hours. Gastrointestinal side effects, most notably diarrhea, occur in up to 80% of patients, resulting in electrolyte imbalances and fluid losses. In the critically ill patient, oral colchicine may not be feasible and is potentially toxic. Renal and hepatic insufficiencies are risk factors for colchicine related neuromyopathy and bone marrow suppression. In addition, potential drug–drug interactions, including macrolide antibiotics, HMG-CoA reductase inhibitors, fibric acid derivatives, verapamil and diltiazem, and cyclosporine may potentiate colchicine toxicities.

A recent study reports equal efficacy in reducing pain of acute gout with low dose colchicine (1.2 mg orally followed in 1 hour by another 0.6 mg orally) to traditional oral loading of colchicine (1.2 mg orally followed by 0.6 mg every hour for 6 hours) [2]. In addition, the gastrointestinal side effects are significantly reduced with the low dose regimen. Thus, if an ICU patient with an acute onset of gout has normal renal and hepatic function and is able to take oral colchicine, the low dose regimen is a reasonable choice. However, if there is renal insufficiency, dose adjustment is necessary and colchicine is probably best avoided if creatinine clearance is less than 10 mL per minute. A more appropriate use of oral colchicine is the prevention of subsequent attacks once the acute attack is treated. Dosages of 0.6 mg orally once or twice a day have been effective (again dose adjustment is necessary based on GFR) [3]. The most common side effects include nausea, diarrhea, and proximal myopathy with elevated creatinine kinase levels. The risk of myotoxicity correlates with a creatinine clearance of less than 50 mL per minute.

Intravenous colchicine has been used in the past for acute gout. However, due to numerous deaths and inappropriate use of the intravenous route, the United States Food and Drug Administration has recommended the discontinuation of production of intravenous colchicine since 2008 and it is unavailable at this time.

Nonsteroidal Anti-inflammatory Drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of acute gout. However, the mechanism of action involves prostaglandin inhibition, which can interfere with gastric mucosal integrity and worsen renal function by reducing renal perfusion in the setting of volume contraction. NSAIDs may also cause other side effects, including decreased coronary flow and mental status changes. Although the cyclooxygenase-2 inhibitor agents offer the possibility of fewer adverse events, their safety profile is based on outpatient experience. Serious adverse effects with these newer agents have been reported. Given the fact that many patients in the ICU have some degree of renal disease and are at risk for gastrointestinal bleeding, NSAIDs are rarely a first-line agent in the treatment of gout in the ICU.

Other Microcrystalline Arthropathies

Although gout is the best-defined and most common crystalline arthropathy, several other crystalline-induced syndromes may mimic gout and cause potential diagnostic confusion. These include calcium pyrophosphate dihydrate (CPPD), BCP-hydroxyapatite, or calcium oxalate crystals.

Pathogenesis

The pathophysiology of these entities appears to be similar to that of gouty arthritis, involving a complex series of biochemical reactions that lead to an inflammatory response within the involved joint or periarticular region. Similar to gout, each of these disorders may be more common in a specific subset of ICU patients.

The acute, self-limited form of CPPD deposition (also known as *pseudogout*) may be precipitated by surgery of any type and is related to downward fluxes in serum calcium levels that lead to crystal shedding into intra-articular spaces. Attacks commonly occur several days postoperatively and often involve the knee or wrist. Severe medical illnesses, such as ischemic heart disease, cerebral infarction, and thrombophlebitis, may also provoke attacks of CPPD arthritis.

Patients on chronic intermittent peritoneal dialysis have a high incidence of acute arthritis that is secondary to CPPD or

BCP-hydroxyapatite deposition in articular cartilage. In contrast, chronic hemodialysis patients are at risk for acute arthritis from calcium oxalate crystals.

Clinical Features

Clinically, each of the above crystalline arthropathies is indistinguishable from acute gout. The presence of radiographic calcification in hyaline or articular cartilage of the involved joint (i.e., chondrocalcinosis) suggests the diagnosis of pseudogout, but the diagnosis is confirmed by visualizing weakly positively birefringent, rhomboid-shaped CPPD crystals within synovial fluid PMN under polarizing microscopy. Calcium oxalate crystals, likewise, are positively birefringent, but they are pleomorphic, bipyramidal, or rod-like in shape. Smaller BCP-hydroxyapatite crystals, however, are not visible under polarizing microscopy, and a presumptive diagnosis is made given the clinical setting, the exclusion of other diagnoses, and the occasional presence of periarticular, amorphous calcifications on radiographs.

Therapy

Therapeutic options are limited in the ICU patient if NSAIDs are contraindicated. Isolated joints can be aspirated and injected with corticosteroids once infection is excluded. Alternatively, a regimen of tapering corticosteroids similar to acute gout is effective. Pseudogout may also respond dramatically to colchicine in dosing similar to gout. Low dose colchicine is also used to prevent recurrent attacks in patients who have frequent events.

Septic Arthritis

Joint infection is the most critical diagnosis to establish and treat in any ICU patient who develops acute mono- or oligoarthritis. A delay in the diagnosis and treatment of septic arthritis may lead to destruction of articular cartilage and loss of joint function. Furthermore, a diagnosis of septic arthritis may help identify and initiate early treatment of the source of septicemia, such as endocarditis (see Chapter 80).

Pathogenesis

Risk factors for development of septic arthritis include diabetes mellitus, age over 80, skin infections, rheumatoid arthritis (RA), intravenous drug abuse, alcoholism, recent joint surgery, low socioeconomic status, and presence of prosthetic joints [4]. In addition, patients in the ICU often have multiple invasive procedures, indwelling lines, or catheters that are potential portals of infection. Whether or not these predisposing factors exist, acute septic arthritis usually develops from hematogenous seeding from another site of infection. Direct inoculation or local extension from adjacent soft tissue infection or osteomyelitis is less common. Prosthetic joints or damaged joints from rheumatoid or osteoarthritis are particularly susceptible to hematogenous seeding. Once an infection is established within a joint, a complex cascade of physiologic responses occurs that leads to a severe inflammatory reaction with subsequent cartilage degradation and bone destruction. The rapidity and severity of this process depends on the virulence of the organism and the length of time delay before appropriate antibiotics are started.

Clinical Features

Clinically, septic arthritis may be indistinguishable from crystalline arthritis or other inflammatory joint diseases. The presentation is often acute and monoarticular with physical findings of warmth, swelling, tenderness, and erythema within the confines of the joint margins, and markedly limited joint motion. The knee, hip, shoulder, elbow, and ankle are the most common joints involved. Atypical joints such as the sternoclavicular, symphysis pubis, or sacroiliac joints are common sites of infection in younger patients, or those with a history of intravenous drug use. Polyarticular infections may occur in 20% of the cases in reported studies [4], particularly in patients with rheumatoid arthritis. Fever is a variable finding and when present, it may be low grade.

High clinical suspicion remains essential to the diagnosis of septic arthritis. Unless physical examination indicates extra-articular features (e.g., cellulitis), any ICU patient with an acutely swollen, painful joint needs a diagnostic arthrocentesis to exclude infection. In the case of suspected cellulitis, appropriate antibiotics should be administered and arthrocentesis performed only if symptoms or findings do not improve within 48 hours. The diagnosis of septic arthritis is supported by an elevated white blood cell count (WBC), ESR, and CRP, but these studies cannot reliably differentiate infection from other inflammatory processes. Conversely, the absence of fever or normal ESR or CRP cannot exclude septic arthritis. Thus, synovial fluid analysis can confirm septic arthritis and identify organisms on Gram's stain or in culture. The fluid should be transferred immediately to the laboratory, both anaerobic and aerobic cultures should be ordered routinely, and special requests for fungus or other organisms that require a special growth medium (e.g., *Neisseria gonorrhoeae*) are ordered if clinically indicated. In addition, synovial fluid analysis for WBC with differential and crystal search may support a diagnosis of infection before microbiology results are available. Although leukocyte counts under 20,000 per µL have been associated with septic arthritis, the WBC generally exceeds 50,000 per µL and on occasion may be as high as 200,000 per µL with a marked PMN predominance. A meta-analysis of various laboratory studies in septic arthritis suggests that the likelihood ratio of septic arthritis increases incrementally with higher synovial leukocyte counts [5]. However, since septic arthritis has been associated with WBC as low as 2,000 per µL to 50,000 per µL, the absolute number cannot differentiate septic arthritis from other inflammatory states such as rheumatoid, psoriatic, or crystalline arthritis.

Although initial radiographs of the infected joint are often normal, baseline x-rays are useful to identify preexisting joint abnormalities and for comparison to identify subsequent changes of septic damage. MRI imaging may be helpful to evaluate joints that are difficult to assess clinically (i.e. spine, sacroiliac, or hip), bone for underlying osteomyelitis, and soft tissue for sinus tracts. Classic late radiographic findings include juxta-articular osteopenia, joint-space narrowing, or subchondral bone loss.

Therapy

Once the diagnosis of septic arthritis is either strongly suspected on clinical grounds or documented by positive Gram's stain or culture, treatment requires adequate drainage in addition to appropriate antibiotics. *N. gonorrhoeae* is the most common cause of septic arthritis in patients under the age of 30, but overall, *Staphylococcus aureus (S. aureus)*, including methicillin resistant *S. aureus* (MRSA), is the most common organism in the immunocompetent patient, followed in frequency by *Streptococcal* species. Together, these Gram-positive organisms made up 91% of septic arthritis in a prospective study [6]. Gram negative and anaerobic organisms occur less frequently but must be suspected in patients at risk (elderly, immunocompromised, recent hospitalization or surgery, prior antibiotics, and possible urogenital or abdominal infections) [4]. In the critically ill patient with multiple risk factors, broad-spectrum antibiotic coverage against staphylococcus and streptococcus, Gram-negative bacteria, and pseudomonas should be initiated until culture results are available. Fungal or mycobacterial septic arthritis is often subacute or chronic and thus unlikely to be

initially considered but remains the possible cause if symptoms persist. *Candida* organisms have caused acute arthritis and the Gram stain may be positive before cultures are available. The duration of antibiotic therapy varies according to the clinical situation, but antibiotics should be continued intravenously for at least 2 weeks. Further route and duration of therapy depend on the specific type and sensitivity of identified organism and the patient's clinical response. However, the length of treatment is usually at least 4 weeks for nongonococcal septic arthritis. Please refer to Chapter 77 for appropriate antibiotic treatment and dosing for presumptive or identified infectious organisms.

Drainage of the infected joint either with serial percutaneous needle aspirations or surgical intervention is also crucial. Since there are no prospective studies comparing these options, controversy exists regarding the optimal approach. The physical removal of inflammatory cells, cellular debris, lysosomal enzymes, and bacterial byproducts reduce the potential damage to the joint. Prosthetic joints and other native joints such as hip, shoulder, wrist, finger, sacroiliac or sternoclavicular joints require immediate surgical intervention, while native septic knees may respond to serial percutaneous needle aspiration. Arthroscopy or arthrotomy has the advantage of more complete debridement of fibrin, infected synovium, and loculations. However, percutaneous drainage may be the only option in a critically ill patient who is unstable for surgery. Indications for surgical intervention include initial delay in diagnosis, established joint damage from RA or osteoarthritis, failure to sterilize the joint fluid after 3 to 5 days of antibiotics, difficult percutaneous aspirations due to loculations, or infection with Gram-negative bacterium. Thus, the ideal approach is to consult both the orthopedist and rheumatologist at the time of diagnosis to decide on optimal management.

The affected joint should be immobilized in functional position in the first few days. Once antibiotics are given and drainage has been performed, early physical therapy with passive range of motion and graduation to active range of motion will improve outcome [7].

Finally, since septic arthritis usually occurs as a consequence of bacteremia from a distant primary source of infection, investigation for these sites must be pursued. Unless an obvious site of local inoculation is present, cultures from blood, urine, sputum, indwelling lines, and catheters should be obtained before the institution of antibiotics. In addition, imaging studies such as echocardiography, tomography (CT), or gallium scanning might locate the source of infection.

Septic Arthritis in the Prosthetic Joint

Although rates of prosthetic joint infections (PJI) are generally quite low, 0.8% to 1.9% and 0.3% to 1.7% for knees and hips, respectively [8], RA patients have an increased risk of developing infected prosthetic joints. Risk factors are similar for native septic arthritis discussed previously as well as a history of prior infection of prosthetic joint at the same site or revision arthroplasty. Early infection, usually within 3 months of surgery, is usually due to *S. aureus* or more virulent organisms from direct inoculation at the time of surgery; chronic infections with less aggressive bacterium including coagulase-negative staphylococci occur often months to years after the replacement. Bacteremia with seeding of a prosthetic joint can occur anytime. Causative organisms for PJI are predominantly Gram-positive cocci (65%); aerobic Gram-negative bacilli and anaerobes contribute 10%, while 20% are polymicrobial infections [8].

Clinical features of acute PJI include localized pain, fever (occurring in < 50%), and elevation of ESR, while more chronic infections may present with only pain and loosening of hardware on radiograph. CRP elevation of more than 5 mg per L has a sensitivity of 95% and specificity of 62% in the diagnosis of PJI [9]. Plain radiographs cannot distinguish aseptic periprosthetic loosening from infection. Computed tomography and magnetic imaging may be distorted by ferromagnetic prostheses. The imaging of choice for the diagnosis of PJI is indium-111 labeled WBC in combination with technetium-99m-labeled sulfur colloid bone scan [10]. Synovial fluid studies are as useful in prosthetic joint infections as native joint infections. However, a synovial fluid WBC more than 1,700 cells per µL from the prosthetic knee joint or more than 4,200 cell per µL from the prosthetic hip joint with predominantly PMNs on the differential is enough to suggest infection [8]. If aspiration is not done before surgery, then intraoperative sampling of multiple periprosthetic tissue sites will increase the yield of an organism. Culture of the removed prosthesis may also provide additional microbial information.

Treatment of suspected PJI should initially cover both Gram-negative and Gram-positive organisms with a regimen such as vancomycin and an aminoglycoside until microbiology results and antibiotic sensitivities are available (see Chapter 77). Initial infectious disease consultation will help guide therapy.

Antibiotics alone without surgical intervention, however, are rarely successful. If the patient is a surgical candidate, options include: (1) resection arthroplasty, (2) one or two stage surgery with prosthesis removal and reimplantation, or (3) surgical debridement with retention of prosthesis with or without long-term oral antibiotic suppression. The first option is rarely performed unless the patient has failed previous surgical attempts at eradicating the infection or is likely to have minimal functional improvement after replacement. Chronic PJI requires resection arthroplasty with one or two stage exchanges. The latter usually entails removal of the infected prosthesis, treatment with antibiotics with or without an antibiotic loaded spacer for a period of 6 to 12 weeks, and then subsequent reimplantation. Debridement with retention of the infected prosthesis is an option only if (i) age of the prosthesis is less than 3 months; (ii) symptoms have been present for less than 3 weeks; (iii) absence of sinus tract communicating with joint space; (iv) no radiographic evidence of prosthetic loosening; (v) infection not involving *S. aureus, Pseudomonas aeruginosa*, enterococcus, fungal or multidrug resistant organisms; and (vi) absence of comorbidities such as diabetes and rheumatoid arthritis [11]. Prolonged oral antibiotics (3 months for hips and 6 months for knees) are recommended in patients treated with debridement with implant retention [8].

Hemarthrosis

In the absence of an underlying inherited disorder of coagulation, hemarthrosis in the intensive care setting is most likely a complication of anticoagulation therapy, most frequently described in patients receiving an oral anticoagulant (sodium warfarin). Since hemarthrosis may occur spontaneously in an anticoagulated patient, a history of trauma is often absent. Clinically, a patient develops a monoarticular, painful, swollen, warm, and tense effusion. A prolongation of coagulation parameters suggests the diagnosis, but diagnostic arthrocentesis is essential to confirm the diagnosis of hemarthrosis and exclude septic arthritis, crystalline disease, or other causes. When performed aseptically and carefully, arthrocentesis is safe and free of significant long-term morbidity. It is unnecessary to reverse the anticoagulant state prior to arthrocentesis.

A precise definition of hemarthrosis has not been established, but the diagnosis is suggested by a synovial fluid hematocrit exceeding 3%. Causes of hemarthrosis other than anticoagulation include trauma (especially with intra-articular fracture), blood dyscrasias, Charcot joint, synovial tumors such as pigmented villonodular synovitis or other primary or metastatic neoplasms, myeloproliferative disease, CPPD

arthropathy, septic arthritis, sickle cell trait or disease, and scurvy.

Despite the fact that hemophiliac patients with repeated hemarthrosis have significant joint abnormalities, an isolated episode of spontaneous hemarthrosis has a benign prognosis. Treatment of hemarthrosis from hemophilia or other bleeding diathesis is discussed elsewhere (see Chapters 108,109, and 114). Management of spontaneous hemarthrosis from anticoagulation consists of immobilization, analgesia, and if possible, temporarily reducing or correcting clotting parameters with fresh frozen plasma if the patient is not at high risk of thromboembolism. If the patient is at high risk (i.e., prosthetic valve), allowing the INR to drift toward the lower therapeutic range is one option. Arthrocentesis may reduce the pressure of joint distension. Once the hemarthrosis improves, close monitoring of coagulation parameters to values within the therapeutic range minimizes the chance of recurrence.

ASPECTS OF RHEUMATIC DISEASES COMPLICATING INTENSIVE CARE PROCEDURES

Difficult endotracheal intubations may be encountered in patients with RA, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), or systemic sclerosis (SSc). Involvement of the cervical spine, temporal mandibular joints, or oral aperture may limit adequate positioning, visualization, or successful endotracheal intubation with conventional techniques. The use of fiberoptic intubation, laryngoscopy, or blind nasotracheal intubation may suffice in some instances (see Chapter 1), although a tracheostomy may be required for satisfactory tracheal cannulation (see Chapter 15), particularly in emergent situations. Potentially more serious neurological sequelae are anterior atlantoaxial subluxation or a staircase cervical subluxation that involves many cervical vertebrae.

The prevalence of atlantoaxial instability in RA patients is estimated to be anywhere from 23% to 60% depending on the subpopulation studied and is associated with duration and severity of disease [12]. This instability also occurs in certain subgroups of patients with JIA and ankylosing spondylitis. Although the majority of patients with cervical spine involvement are asymptomatic, forced manipulation of the neck (e.g., during intubation, endotracheal suctioning, nasogastric tube placement, bronchoscopy, or endoscopy) may precipitate symptoms and signs of spinal cord compression.

Cervical instability and dislocations most commonly occur at the atlantoaxial (first and second cervical vertebrae) junction due to laxity or erosion of the transverse ligament caused by synovitis. Subsequently, the odontoid (superior peg of the second cervical vertebra) moves more freely and can protrude posteriorly, particularly during neck flexion, and compress the spinal cord, lower medulla, or vertebrobasilar arteries. Fracture or erosive destruction of the odontoid may allow the atlas (first cervical vertebra) to slide posteriorly on the second cervical vertebrae, a process termed posterior atlantoaxial subluxation. Destruction of the lateral atlantoaxial joints and of the bones of the foramen magnum may allow the axis to sublux cephalad, so-called vertical subluxation. Symptoms suggestive of cervical myelopathy include Lhermitte's sign, neck pain radiating up to the occiput, paresthesias in the hands or feet, loss of arm or leg strength, and urinary incontinence or retention.

Patients at risk are identified with lateral cervical spine radiographs in flexed and extended views. The normal distance between the odontoid process and the arch of the atlantis is less than 4 mm. If this distance is exceeded, care should be taken to avoid sudden or forced neck flexion during any intensive care procedure. A soft cervical collar to maintain the neck in slight extension helps prevent sudden forced flexion and is a reminder to all caregivers that any neck manipulation should proceed with caution. Open-mouth posterior-to-anterior views will exclude odontoid fracture and severe subluxation, but MRI scanning is the best imaging procedure to exclude cord compression.

In patients with ankylosing spondylitis where multilevel cervical fusion exists, large anterior cervical osteophytes can prevent adequate visualization of the larynx or successful endotracheal intubation. Fixed cervical flexion deformities can hinder appropriate neck positioning for intubation. The ankylosed spine is often osteoporotic and brittle. Minor forces in flexing or extending the neck can result in inadvertent fracture. Thus, plain radiograph imaging with lateral views before any procedure can help establish potential barriers to endotracheal intubation and the need for fiberoptic nasotracheal intubation [13].

Patients with JIA (and RA more rarely) may have established micrognathia due to temporomandibular joint disease that restricts lower jaw motion and limits access to the oropharynx. Micrognathia may also cause upper respiratory tract obstruction and sleep apnea, both of which occur more commonly in patients with JIA. In contrast, patients with systemic sclerosis (SSc) may have facial tissue fibrosis and atrophy that reduce the oral aperture and make orotracheal intubation impossible. In these situations, early awareness of the need for nasotracheal intubation will prevent potential complications in routine or emergency endotracheal intubation.

Nearly 50% to 75% of patients with longstanding RA have involvement of the cricoarytenoid joints on CT scans, but only half have symptoms [14]. These synovial joints allow adduction and abduction of the vocal cords. Symptoms of cricoarytenoid involvement include throat pain, sensation of a foreign object in the throat, odynophagia, dysphagia, hoarseness, shortness of breath, and stridor. As a result of acute or chronic inflammation, the vocal cords may become fixed in a position of adduction, resulting in upper airway obstruction and respiratory failure. The diagnosis may be made and distinguished from recurrent laryngeal nerve paralysis, tumor, and thyroiditis by visualizing the vocal cords either by indirect laryngoscopy or fiberoptic nasopharyngoscopy. In the patient with chronically restricted motion of the cricoarytenoid joints, a superimposed insult, like an upper respiratory tract infection or trauma from intubation, may cause sufficient soft tissue swelling to cause laryngospasm or airway obstruction. Treatment of life-threatening airway obstruction includes establishing an airway by cricothyroidotomy or tracheostomy, high-dose systemic corticosteroids, systemic antirheumatic therapy, and topical aerosolized corticosteroids.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disorder that affects synovial joints and extra-articular organ systems. The patient with RA may require admission to the ICU because of airway obstruction due to cricoarytenoid arthritis or atlantoaxial subluxation (discussed previously); septic arthritis; respiratory distress from large pleural effusions or parenchymal lung disease; cardiac dysfunction due to pericardial, myocardial, or endocardial involvement; necrotizing vasculitis; or mononeuritis. The approach to the RA patient in the ICU includes knowledge of the diverse complications of rheumatoid disease and the potential toxicities of RA medications including NSAIDs, corticosteroids, traditional disease modifying agents, and the newer biologic agents.

Pathogenesis

Rheumatoid arthritis is characterized by chronic synovial inflammation with subsequent articular cartilage and bone

destruction in a genetically susceptible host. The initial triggering antigen, whether exogenous or self, has not been identified, but the subsequent CD4 T-cell activation initiates the process of recruitment of other cells to the joint space, including macrophages, neutrophils, and B cells. Fibroblast-like and macrophage-like synovial cells perpetuate synovial inflammation through elaboration of cytokines that have paracrine and autocrine activity. In addition to cytokines, the products of several cell types also induce adhesion molecules and stimulate angiogenesis. Activated synovial cells also release metalloproteinases responsible for degradation of articular cartilage and erosion of bone.

Joint Infections Complicating Rheumatoid Arthritis

One indication for admission of the RA patient to an ICU is sepsis, particularly involving joints. RA patients are more susceptible to developing septic arthritis, often polyarticular and more severe than in patients without RA. A variety of factors, including immunosuppressive drugs, general debility, immobility, and cutaneous ulcers predispose the rheumatoid patient to developing bacterial infections in other sites, which hematogenously seed inflamed rheumatoid joints. Normal protective mechanisms, PMN leukocyte bacterial killing, PMN chemotaxis, and complement and serum bactericidal activity are all decreased in the rheumatoid joint. Although joint sepsis after arthrocentesis or intra-articular steroid injection is a rare complication, infection has been reported in this context and may be more resistant to treatment.

A delay in diagnosing joint sepsis in RA patients may also contribute to their increased morbidity and mortality. Other factors include: 1) masking of joint pain and inflammation by NSAIDs, corticosteroids, and immunosuppressive agents; 2) generalized debility and malnutrition; and 3) attributing the joint inflammation to RA rather than infection by the patient or physician. Failure to recognize septic arthritis complicating RA may have disastrous effects. When a single or few joints are more inflamed than others in a rheumatoid patient, joint sepsis should be excluded by arthrocentesis, Gram's stain, and cultures of synovial fluid, blood, and other appropriate sites guided by the patient's signs and symptoms. Inspection of the skin for a possible portal of bacterial entry and a thorough general examination are of the utmost importance.

The microbiology of septic arthritis complicating RA includes a wide range of organisms, but in approximately 80% of cases, the organism is *S. aureus*. Streptococcal species are also common pathogens. Gram-negative organisms (*Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, and others), anaerobes, fungi, mycobacterium, and polymicrobial infection, have all been reported as causes of septic arthritis in the rheumatoid joint.

Management of septic arthritis in a rheumatoid patient is identical to patients without RA. However, the septic rheumatoid joint more frequently fails percutaneous needle aspiration. Early surgical drainage with synovectomy may be the preferred treatment since there is more proliferative synovitis and an increased tendency for loculations to develop in this population.

Pulmonary Involvement in Rheumatoid Arthritis

The respiratory system in the patient with RA can be involved in numerous ways, including upper airway, bronchi, pleura, parenchyma, vasculature, and diaphragmatic muscles. Pulmonary infections are common, particularly in the patient with poor mucociliary clearance, ineffective cough, on immunosuppressive therapy, or with associated Sjögren's syndrome. Table 193.1 summarizes respiratory tract involvement in RA and other connective tissue disorders. In addition, certain antirheumatic drugs are associated with potential pulmonary toxicities. Angioedema and bronchospasm induced or aggravated by aspirin or other NSAIDs is most common followed by hypersensitivity pneumonitis from methotrexate or sulfasalazine, or interstitial fibrosis from methotrexate.

Pleural Disease

Pleuritis and interstitial disease are the most common pulmonary manifestations of RA, and the former is most common in a subset of male patients who are seropositive and have nodules. Although involvement may be asymptomatic, acute febrile pleurisy or large pleural effusions impairing respiratory function may occur and result in ICU admission. The differential diagnoses of the pleural effusions include malignancy, pulmonary infarction, viral or bacterial infection, tuberculosis, and empyema. Infectious empyema occurs with increased frequency in patients with preexisting rheumatoid pleural effusions and should be suspected in debilitated, anemic, or hypoproteinemic patients who have been treated with corticosteroids and have persistent fever and pleural effusions. In patients on anti–tumor necrosis factor alpha (anti-TNF-α therapies), reactivation of (or new infection with) tuberculosis is of major concern and needs to be excluded with pleural biopsy.

Pleural effusions and sterile empyemas associated with RA are exudative and have characteristic features: elevated lactic dehydrogenase (often > 700 IU per L), total protein (> 4 g per dL), low glucose (< 40 mg per dL), and pH < 7.2. Other characteristics include clear yellow to green-yellow appearance, white blood cell count of 100 to 7,000 cells per μL (predominantly lymphocytes), reduced complement levels, cholesterol crystals, and immune complexes [15]. Chylous effusions may occur if necrotic subpleural nodules rupture into the pleural space.

Once infections including tuberculosis and malignancy are excluded, symptomatic pleural effusions are managed with NSAIDs and thoracentesis. In recurrent pleuritis or sterile empyema, intrapleural corticosteroids, systemic corticosteroids in moderate doses, and additional disease modifying agents are recommended. Rarely, surgical pleurodesis or decortication is required if chronic adhesive fibrothorax develops. There are no prospective trials to evaluate the efficacy of many of these recommendations [15]. High-dose corticosteroid therapy may not be effective and carries an increased risk of an empyema.

Lung Disease

ILD occurs in up to 40% to 60% of patients with RA depending on the subpopulations studied and screening tests used to make the diagnosis. In a prospective European study of newly diagnosed RA patients, the annual incidence was 4 in 1,000 patients but over 20 years, mortality was over 75% in those patients with interstitial lung disease, with the majority of deaths due to ILD [16]. Thus after infection, pulmonary disease is the second most common cause of mortality in RA patients. Pathologically, usual interstitial pneumonia(UIP) is more common than nonspecific interstitial pneumonitis (NSIP). Lymphocytic interstitial pneumonitis (LIP), organizing pneumonia (OP), and acute interstitial pneumonia are less common.

Symptoms include dyspnea on exertion, cough, and chest discomfort. Physical and laboratory findings include dry crackles, diminished diffusion capacity, and restrictive physiology, as well as desaturation with exercise. Chest radiographs may show an interstitial pattern, but high-resolution CT scanning (HRCT) is a more sensitive test in assessing pneumonitis and fibrosis. Bronchoalveolar lavage (BAL) is not particularly helpful except to rule out infection, while thoracoscopy guided lung biopsy provides the best pathologic details. Treatment of ILD due to RA is extremely challenging. Some patients may respond

TABLE 193.1

RESPIRATORY INVOLVEMENT IN CONNECTIVE TISSUE DISEASES

	Common	Rare (< 10%)
Upper airway involvement		
Cricoarytenoid arthritis	RA	SLE
Laryngeal nodules	RA	
Bronchial tree		
Obliterative bronchiolitis		RA
Bronchiectasis	SSc	RA, SS, SLE
Follicular or constrictive bronchiolitis		RA, SS
Bronchiolitis obliterans with organizing pneumonia	RA	SLE, PM/DM
Parenchyma		
Interstitial lung disease	RA, SSc, SS, PM/DM	SLE
Acute pneumonitis		SLE, PM/DM
Bronchiolitis obliterans with organizing pneumonia	RA	PM/DM
Cryptogenic organizing pneumonia		RA, SLE, PM/DM, SSc
Rheumatoid nodules ± cavitation	RA	
Aspiration	SSc, PM/DM	RA
Drugs: methotrexate, sulfasalazine, minocycline		
Infections	All	
Pleura		
Pleuritis	RA, SLE	
Pleural effusions	RA, SLE	
Pleural thickening	RA	SLE
Respiratory muscle disease		
Myositis	PM/DM	RA
Diaphragm dysfunction	PM/DM	SLE
Vascular		
Pulmonary hypertension	SSc	SLE, RA, PM/DM, APS
Vasculitis	SLE	PM/DM, RA
Diffuse alveolar hemorrhage		SLE, RA, PM/DM, APS
Pulmonary Embolism	APS, SLE	

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SS, Sjogren syndrome; PM/DM, polymyositis/dermatomyositis; APS, antiphospholipid syndrome.

to corticosteroids alone but the progressive nature of the disease may require treatment with cytotoxic agents although it is unclear which immunosuppressant is most effective [17]. In those patients with ground glass opacities on HRCT scanning, IV cyclophosphamide is being used increasingly, although no large controlled trial exists to support this approach. Case reports on the use of biologic agents are conflicting.

Other less common manifestations of rheumatoid lung disease may require treatment in the ICU when patients develop respiratory distress. These include bronchiolitis obliterans with organizing pneumonia (BOOP), obliterative bronchiolitis (OB), cryptogenic organizing pneumonia, pulmonary vasculitis, spontaneous pneumothorax, and lung toxicity secondary to antirheumatic therapy. It is particularly important to distinguish BOOP from ILD and OB, and only lung biopsy will provide histological distinction.

Obliterative alveolitis is often characterized by the abrupt onset of dyspnea and a dry cough with inspiratory crackles, sometimes with a mid-inspiratory squeak, a clear chest radiograph or finding of hyperinflation, irreversible airflow obstruction at low volumes on pulmonary function testing, mild-to-moderate arterial hypoxemia with a respiratory alkalosis, and progressive obliteration of small airways (1 to 6 mm in diameter) with constrictive bronchiolitis [18]. The prognosis is generally poor with a fairly rapid rate of progressive airflow obstruction. Despite the lack of adequate therapeutic trials, when patients present with rapidly progressive deterioration, recommendations based on expert opinion include bronchodilators and inhaled and oral corticosteroids (1 to 1.5 mg per kg per day). Macrolides, pulse intravenous cyclophosphamide, or etanercept (with methotrexate) may be considered as second-line therapy [18]. Progression to respiratory failure is common. In contrast, BOOP is more responsive to corticosteroid therapy.

Rarely, chronic vasculitis may involve pulmonary as well as bronchial arterioles and result in pulmonary hypertension and cor pulmonale. Therapy consists of corticosteroids in combination with cytotoxic agents (see Chapter 196).

Although pulmonary manifestations of RA are frequent, they are rarely the primary reason for admission to the ICU. Infectious pneumonia is particularly frequent and the major cause of mortality in rheumatoid patients. Since the advent of TNF-α agents, atypical infections and reactivation of tuberculosis have been of great concern.

Rheumatoid Cardiac Involvement

RA may involve all structures of the heart as a result of granulomatous proliferation or vasculitis. Pericarditis, myocarditis,

endocarditis (valvulitis), coronary arteritis, aortitis, and cardiac conduction abnormalities have all been reported. Cardiac involvement may be the principal reason for intensive care hospitalization, or may complicate the course of the rheumatoid patient hospitalized in the ICU for other medical or surgical problems.

Pericarditis, the most common of the rheumatoid cardiac manifestations (approximately 50% by autopsy studies) rarely causes impairment of left ventricular function. However, constrictive pericarditis or a large pericardial effusion may rarely cause cardiac tamponade. The pericardial fluid has the same characteristics as pleural fluid (see the section Pulmonary Involvement in Rheumatoid Arthritis). Pericarditis generally responds to the administration of 30 to 40 mg prednisone per day over a several-week period. Corticosteroids alone are less likely to be effective in the setting of cardiac tamponade. Pericardiocentesis should be performed early if tamponade is suspected (see Chapters 7 and 35) or if there is a question of septic or suppurative pericarditis. Aspiration of pericardial fluid may temporarily improve cardiac function, but often the viscosity of the fluid, loculations, and thickness of the pericardium necessitate pericardiectomy. In cases of constrictive pericarditis, pericardiectomy is the only effective therapy.

The myocardium may be affected by granulomatous inflammation and by vasculitis. Cardiac conduction abnormalities, including complete heart block, may develop because of subcutaneous nodules. Arteritis may affect the coronary arteries and the aorta. In patients with active systemic vasculitis, coronary arteritis may be the cause of myocardial infarction. Involvement of the aorta, either by rheumatoid granulomas or inflammation of the aortic vasa vasorum, may result in dilatation of the aortic root and aortic valvular insufficiency.

Rheumatoid arthritis patients die prematurely from cardiovascular events that include (i) ischemic heart disease, often silent; (ii) congestive failure, often in the setting of preserved ejection fraction; and (iii) sudden death. When compared to non-RA patients, these increased cardiovascular complications are not explained by traditional risk factors alone. Other factors, including poor primary or secondary preventive care and comorbid conditions along with the chronic inflammatory or immunologic state contribute to premature cardiac deaths [19]. Thus, in the ICU setting, silent cardiovascular disease with atypical presentations must be considered in the rheumatoid patient.

Rheumatoid Vasculitis

The vasculitis that complicates RA is a panarteritis with mononuclear cell infiltrates in all layers of the involved blood vessels, fibrinoid necrosis in active lesions, and thrombosis associated with intimal proliferation. Rheumatoid vasculitis tends to occur in patients with severe deforming RA, subcutaneous nodules, and high-titer rheumatoid factor, and in patients with Felty's syndrome. The clinical features of rheumatoid vasculitis are variable and include palpable purpura, cutaneous ulceration including pyoderma gangrenosum, distal arteritis ranging from fingernail-fold infarcts and splinter hemorrhages to digital gangrene, and arteritis of major organs including the bowel, kidneys, heart, lungs, liver, spleen, pancreas, and components of the nervous system in a manner similar to polyarteritis nodosa. Severe necrotizing forms of rheumatoid vasculitis, manifested as digital gangrene, intestinal bleeding or perforation, myocardial or renal infarction, and mononeuritis multiplex, are associated with a poor prognosis and are treated aggressively in a manner similar to that of polyarteritis and Wegener's granulomatosis (see Chapter 196) with high-dose corticosteroids, cytotoxic agents, and occasionally plasmapheresis.

Neurologic Complications of Rheumatoid Arthritis

All components of the nervous system can be affected by RA. The brain and meninges, spinal cord, peripheral nerves, and muscles may be involved with granulomatous inflammation in the form of rheumatoid nodules or vasculitis; the spinal cord and cranial and peripheral nerves may also be compressed by skeletal and soft tissue structures, and the nervous system may be affected by hyperviscosity syndrome and medications.

Spinal cord compression is one of the most common neurologic complications in patients with RA is discussed in previous section. Manifestations that require immediate intervention include the sensation of anterior instability of the head during neck flexion, drop attacks, loss of urinary bladder and anal sphincter control, dysphagia, vertigo, hemiplegia, dysarthria, nystagmus, changes in level of consciousness, and peripheral paresthesias without evidence of a peripheral cause. Although RA patients may have radiographic evidence of cervical subluxation without symptoms, once signs of cord compression become apparent, myelopathy may progress rapidly. For patients with manifestations of spinal cord and brainstem compression, surgical reconstruction of normal alignment and stabilization are treatments of choice. For the nonsurgical candidate, a firm collar can be used in an effort to immobilize the neck and prevent further subluxation.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by excessive autoantibody production and immune complex deposition in multiple organ systems. The clinical result of these varied immune abnormalities is a disease with tremendous variation in signs and symptoms that range from arthralgias, rash, and fatigue to life-threatening renal, central nervous system (CNS), cardiac, pulmonary, or hematological manifestations. Diagnosis of SLE is based on the clinical criteria set forth by the American College of Rheumatology [20]. Mortality of SLE patients admitted to the ICU is much higher than the general ICU population (47% vs. 27%) [21]. In the ICU patient with established SLE, it is essential to differentiate problems caused directly by SLE activity from those with secondary causes such as infections, drug-induced lupus, NSAID-induced renal dysfunction, aseptic meningitis, and corticosteroid-induced psychosis. Diseases associated with SLE include avascular necrosis, hypertensive encephalopathy, pseudotumor cerebri, amyloidosis, myasthenia gravis, and thrombotic thrombocytopenic purpura. In ICU patients without a prior history of autoimmune disease, SLE should be considered in the differential diagnosis of patients presenting with acute renal failure, seizures, myocarditis, acute pulmonary deterioration, hemolytic anemia, or thrombocytopenia.

Renal Disease

Renal involvement is the major cause of disease-related mortality in SLE patients. The frequency of renal involvement ranges from 38% to nearly 80% depending on definition, but clinical lupus nephritis (LN) occurs in approximately 50% of the patients. Advances in diagnostic and therapeutic modalities have dramatically improved the survival of lupus patients with renal disease. Glomerulonephritis and progressive renal failure, however, remain major sources of morbidity and mortality. LN constitutes approximately 3% of all end-stage renal failure in

patients on dialysis or requiring transplantation. Recent data from one transplant group with predominantly white patients found no difference in overall 15-year patient survival (80%) and graft survival (69%) in SLE patients compared with controls [22]. Early graft thrombosis occurred more frequently in patients with antiphospholipid antibodies (APAs) and recurrence of LN was around 8% [23].

Classification of lupus-associated glomerulonephritis (GN) is based on histopathologic, immunofluorescent, and electron microscopic changes according to the 2003 revised classification by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classification [24]. The classification includes: Class I: mesangial GN; Class II: mesangial proliferative GN; Class III: focal proliferative GN; Class IV: diffuse proliferative GN with two subclasses, segmental and global; Class V: membranous GN; and Class VI: advanced sclerosing GN. Renal lesions are commonly pleomorphic, vary from one glomerulus to another, and temporally transition from one class to another over time. The tubulointerstitium and vasculature are often involved. Semiquantitative scoring to define activity and chronicity may provide information on prognosis and guidelines for therapeutic options. In particular, the presence of proliferative lesions and chronic lesions are associated with greater mortality.

The clinical manifestations of renal involvement vary from rapidly progressive renal failure with attendant fluid overload, to congestive heart failure or accelerated hypertension, and are common events precipitating an ICU admission. A sudden deterioration in an SLE patient's renal function warrants careful consideration of other causes of acute renal insufficiency (see Chapter 73) before attributing the deterioration to active SLE. In particular, hypovolemia, drug-induced interstitial nephritis or renal insufficiency, renal vein thrombosis, and contrast-induced acute tubular necrosis must be excluded. Physical examination may reveal evidence of SLE activity in other organ systems. Laboratory studies should include routine tests to assess renal status and fluid balance, and immunologic studies, including double-stranded DNA (dsDNA) antibody, total hemolytic complement, third (C3) and fourth (C4) complement components, and ESR. Active serologies suggest SLE flare, but normal values do not exclude active disease.

Management of LN depends on the patient's renal histopathology and functional parameters. Thus, a patient with mesangial glomerulonephritis with normal creatinine clearance requires no specific therapy, whereas a patient with increasing azotemia, active urinary sediment, and impaired clearance requires aggressive therapy. It is now established that in patients with severe glomerulonephritis (ISN/RPS class III or IV), the combination of high dose prednisone with monthly intravenous pulse cyclophosphamide (IVCY) for 6 months followed by quarterly infusions for additional 6 months stabilizes renal function and improves survival. This regimen is the standard for comparison in all other LN drug trials [25,26]. In the past few years, several trials in different populations have documented the equivalency of mycophenolate mofetil (MMF) up to 3 g per day to monthly IVCY as induction therapy for class III, IV, or V LN [27]. More recently, a large international trial conducted by the ALMS group (Aspreva Lupus Management Study) confirmed this equivalence of both induction regimens at the end of 24 weeks with a response rate of 56% in each group [28]. However, only 8% from either treatment group reached complete remission. This study also supported the racial and ethnic differences in LN and the response to therapy reported in other studies. Patients of Hispanic and African descent had a much better response to MMF than IVCY (60% vs. 38%), while whites and Asian patients responded equally to either regimen. The risk for gonadal failure was less with MMF but other toxicities such as infections were similar. Given the currently available evidence, it appears that MMF and IVCY are equivalent induction therapies for severe LN. Durability of remission is being assessed in a continuation of the ALMS trial in which responders were randomized to either MMF or azathioprine (AZA) for maintenance therapy [28]. Another recent study demonstrated better efficacy and fewer long-term toxicities in maintenance therapy with AZA or MMF rather than the traditional quarterly IVCY after initial monthly IVCY induction [29].

In an acutely ill ICU patient with LN and/or other organ system involvement, IVCY along with pulse IV methylprednisolone at 500 to 1,000 mg daily for 3 days may be the regimen of choice since many of the studies have not stratified for disease severity. The protocol for administration of IVCY therapy is outlined in Table 193.2. Dose adjustments for renal insufficiency are outlined and subsequent monthly dosing is based on nadir white blood cell counts. Another option for IVCY induction is the low dose regimen from the Euro-Lupus Nephritis Trial, which demonstrated equal efficacy and less gonadal toxicity between low dose IVCY (500 mg every 2 weeks for six doses) and high dose IVCY (500 to 750 mg per M^2 with maximum of 1,500 mg, monthly for 6 months, followed by every 3 month infusion until a year) [30]. Both groups then received AZA at 2 mg per kg per day for maintenance. The long-term outcomes measured by death, end-stage renal disease, and doubling of serum creatinine were similar in both groups after 10 years [31].

TABLE 193.2

INTRAVENOUS CYCLOPHOSPHAMIDE THERAPY (IVCY)

1. Initiate IV hydration at 200–500 mL/h
   Normal or $^1/_2$ NS for 1 L over 1–2 h if CrCl > 50 mL/min and depending on cardiac status. (If medical status prevents adequate hydration, MESNA can be substituted—see below.)
2. Antiemetic treatment:
   a. Ondansetron, 8 mg IV < 30 min (or PO < 60 min), prior to CY and then 8 mg every 8 h for 24 h
   b. Granisetron, 1–2 mg IV < 30 min (or < 60 min PO) prior to CY and then every 12 h PO for 24 h
3. MESNA (for CrCl < 50 mL/min or inadequate prehydration due to cardiopulmonary status)
   Give 60% of total CY dose in divided doses: Infuse over 15 min 20% of CY dose (mixed in 50 mL of D_5 W) 30 min prior to CY and repeat same doses 4 and 8 h following CY.
4. Cyclophosphamide: Initial dose is 500–750 mg/M^2 in 250 mL NS over 60 min. Subsequent dose is based on nadir WBC obtained at days 7, 10, 14 after infusion.
   Dose adjustments
   a. CrCl 10–50 mL/min: 75% of CY dose
   b. CrCl < 10 mL/min: 50% of CY dose
   c. Hemodialysis patients: 50% of CY dose after dialysis
   d. Subsequent month dose: increase or decrease by 10%–20% of previous dose
5. Posthydration fluid is identical to prehydration. Monitor adequate urine output and encourage frequent voiding for 24 h after IVCY. In patients without indwelling Foley catheter, avoid CY infusion after 4 pm to reduce prolonged bladder contact with CY metabolites over night.

CY, cyclophosphamide; D_5 W, dextrose 5% in water; IV, intravenous; MESNA, sodium 2-mercaptoethane sulfonate, NS, normal saline; PO, by mouth; WBC, white blood cells.

Membranous GN (Class V), which constitutes 20% of LN, is less aggressive than Class IV GN. While renal survival rate is at 80% at 10 years, it is still associated with significant comorbidities of hyperlipidemia, cardiovascular and thromboembolic diseases [32]. Angiotensin-converting enzyme (ACE) inhibitors have been used successfully to reduce proteinuria. Treatment with corticosteroids, AZA, and cyclosporine has been studied in small series. More recently, the pooled subset of Class V patients from two prospective randomized studies on treatment of GN demonstrated equivalent efficacy and safety profile of MMF and IVCY [33]. Adjunctive renoprotective therapies that include aspirin, statins, ACE inhibitors, or angiotensin receptor blockers should also be instituted.

Advances in biologic therapies for RA and psoriatic arthritis have also stimulated investigations for SLE. Initial open label studies and case reports suggest promising results with the use of rituximab (RTX), an anti-CD20 B-cell depleting monoclonal antibody, for reducing SLE activity. Surprisingly, a randomized trial comparing RTX to placebo with a background of MMF for active proliferative LN revealed no additional benefit, and another study on active nonrenal SLE was also negative [34,35]. Trials of other potential therapies are underway, including a human monoclonal against B-lymphocyte stimulator (BLyS).

Neuropsychiatric Disease

Neuropsychiatric systemic lupus erythematosus (NPSLE), which encompasses involvement of the central, peripheral, and autonomic nervous systems along with psychiatric syndromes, occurs in 25% to 80% of SLE patients depending on the criteria applied or methods used for diagnosis. Although NPSLE was considered a poor prognostic indicator in the older literature, it does not seem to have significant impact on survival rates. Active CNS disease contributed primarily or secondarily to death in only small percentage of patients.

Neuropsychiatric manifestations of SLE can be classified into central versus peripheral nervous system involvement. Due to the limitations of the ACR classification criteria of CNS involvement, an ad hoc neuropsychiatric lupus nomenclature committee of the American College of Rheumatology defined 19 manifestations that included 12 in the CNS and 7 in the peripheral nervous system [36] (Table 193.3). The wide range of prevalence for the more diffuse CNS syndromes (cognitive dysfunction, anxiety, acute confusional states, and psychosis) and headache is due to the definition, criteria, or diagnostic parameters used in reported studies. This proposed nomenclature attempts to define the spectrum of NPSLE but is not a substitute for clinical diagnosis. An individual SLE patient may have multiple neuropsychiatric manifestations and these can develop prior to the formal diagnosis of SLE or during an inactive disease state. Frank psychosis is relatively rare, estimated at 5%. Often, it is difficult to separate active lupus psychosis from other causes such as functional disorders, uremia, illicit drugs, metabolic disturbances, medications, or infections.

Focal central nervous system disease, including seizures that occur in 15% to 35% of SLE patients, can antedate the diagnosis of SLE or develop any time during the disease course. Grand mal seizures are the most common, but essentially all types have been reported. Secondary causes of seizures must be sought since in several prospective studies of SLE patients with neurologic events, a majority of seizures were due to associated infection, uremia, hypertension, and metabolic abnormalities.

Cerebrovascular accidents (5% to 18%) include infarctions secondary to intracranial hemorrhage or arteritis, thrombosis from lupus anticoagulant (LAC) or APA-associated hypercoagulable states, or embolism from Libman-Sacks endocarditis. Movement disorders including chorea, ataxia, and hemiballismus are rare (< 1%) [37]. Transverse myelitis is an unusual but devastating complication of SLE characterized by acute or subacute paraplegia or quadriplegia associated with sensory level deficit and loss of sphincter control. Cerebrospinal fluid (CSF) analysis reveals pleocytosis, low CSF glucose, and high CSF protein. T2-weighted magnetic resonance imaging (MRI) usually demonstrates increased signal intensity and cord edema. Meningitis, usually infectious, may develop in SLE patients. However, aseptic meningitis can be idiopathic or secondary to administration of ibuprofen or AZA.

Peripheral nervous system syndromes include cranial neuropathies (4% to 49%) such as facial palsies and ocular muscle dysfunction. Pure sensory or motor abnormalities based on electromyography/nerve conduction studies (EMG/NCS) occur in up to 47% but plexopathy, Guillain-Barré syndrome, and autonomic neuropathy are rare.

The differentiation of NPSLE from other CNS disorders is difficult and remains a process of elimination. CSF pleocytosis and low glucose require exclusion of infections. Electroencephalography generally reveals diffuse brain wave slowing, but focal activity suggests seizures. Serum antiribosomal P antibodies are associated with lupus psychosis. The gold standard for imaging the central nervous system in SLE is conventional MRI with gadolinium. CT scans are less sensitive and should be reserved for patients in whom MRI is contraindicated or for emergent situations to document bleed, infarct, cerebral edema, or masses. Focal lesions in the subcortical white matter

TABLE 193.3

NEUROPSYCHIATRIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Central nervous system
Diffuse neuropsychiatric syndromes
Cognitive dysfunction (50%–80%)
Anxiety disorders (7%–70%)
Mood disorders (14%–57%)
Psychosis as defined by *DSM-IV* related to medical condition (5%–8%)
Acute confusional state (4%–7%)
Focal neurological syndromes
Headache (24%–72%): range from migraine, tension, or benign intracranial hypertension
Seizures (15%–35%): grand mal, petit mal, temporal lobe, focal
Cerebrovascular disorders (5%–18%): infarcts, transient ischemic attacks
Movement disorders (< 1%): chorea
Transverse myelitis (< 1%)
Demyelinating syndrome (< 1%)
Aseptic meningitis (< 1%)
Peripheral nervous system
Peripheral neuropathy
Polyneuropathy (3%–28%)
Mononeuropathy, single or multiplex
Plexopathy (< 1%)
Cranial neuropathies (4%–49%)
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) < 1%
Autonomic neuropathy (< 1%)
Myasthenia gravis (< 1%)

Adapted from The ACR nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 42:599–608, 1999; Hanly JG. Neuropsychiatric lupus. *Rheum Dis Clin N Am* 31:273, 2005.

are the most common MRI findings and correlate with ischemic changes. Changes in the gray matter that brighten on T2-weighted imaging suggest more acute events and may improve with therapy. However, it is often difficult to distinguish acute from chronic MRI lesions, and subcortical lesions are found in up to 50% of patients without any neuropsychiatric symptoms. Angiography is invasive and rarely results in an accurate diagnosis of active CNS lupus. Since the sensitivity of MRI in patients with cognitive or affective symptoms is low, additional imaging with single-photon emission computerized tomography (SPECT), which measures functional cerebral blood flow, is attractive. Although sensitivity is high (positive in 86% to 100% of patients with major NPSLE manifestations), specificity is low since nearly half of SLE patients without neuropsychiatric involvement have positive SPECT scans [38]. Magnetic resonance angiography is not sensitive enough to delineate the smaller vessels involved in NPSLE. Newer imaging techniques such as magnetic resonance spectroscopy, magnetic transfer imaging, and perfusion and diffusion weighted imaging are still viewed only as research tools and their roles in assessment of NPSLE remain to be determined.

Management of SLE patients with neuropsychiatric manifestations should focus on specific neurologic symptoms. Non-SLE causes of CNS disease, including infections, uremia, hypertension, metabolic disturbances, hypoxia, or drug toxicities, must be identified and treated appropriately. If steroid psychosis is suspected, a brief doubling of the steroid dose for 3 days may exclude the possibility of a diffuse CNS syndrome. If no improvement or evidence of active lupus is noted, the steroid dose should be tapered. Seizures are treated with appropriate anticonvulsant medications. Status epilepticus is treated with anticonvulsants and high-dose steroids. Psychotic patients should receive antipsychotic agents. High-dose steroids have been recommended for neuropsychiatric lupus; dosages range from 1.0 to 1.5 mg per kg per day, or its equivalent. In severe cases, pulse IV methylprednisolone in a dose of 1,000 mg per day for 3 days is preferred. As for immunosuppressive agents, few prospective studies of treatment of NPSLE have been performed. A recent Cochrane database review of therapy for neuropsychiatric lupus found only one controlled clinical trial that suggested better outcomes with monthly IVCY than steroids alone [39,40]. Limited case reports of rituximab therapy in NPSLE suggest efficacy but no randomized studies are available. Transverse myelitis has been treated successfully with pulse methylprednisolone, IVCY, and plasmapheresis.

Pulmonary Disease

The pleuropulmonary manifestations of SLE are common and can involve the pleura, parenchyma, vasculature, diaphragm, or airways (see Table 193.1). Acute pulmonary symptoms can be the initial presentation of SLE that results in an ICU admission, while the prevalence of long-term lung damage (11.6% by 10 years of disease duration) can contribute to the SLE morbidity and mortality [41].

Pleuritis with or without effusions has been reported in 30% to 50% of patients with SLE, depending on the method of study (i.e., clinical history, radiograph findings, or autopsy findings) [42]. Pleural effusions are usually small and bilateral, but massive collections can occur. Thoracentesis is indicated when the etiology of the fluid is uncertain or if respiratory compromise is present. Pleural fluid is characteristically exudative with high protein, pH more than 7.35, and glucose normal or slightly decreased in contrast to the uniformly low glucose and pH seen in rheumatoid pleural effusions. White blood cell counts are elevated and consist predominantly of PMNs. The presence of lupus erythematosus cells on Wright stain is infrequent but highly specific for SLE. Antinuclear antibodies (ANAs) are frequently present in pleural fluids. Mild pleuritis usually responds to NSAIDs or low-dose corticosteroids (0.5 mg per kg per day prednisone or its equivalent). The latter is used only after infection has been excluded.

Acute lupus pneumonitis (ALP), although uncommon (0% to 14%), can be life threatening [42] and may be the initial presentation of SLE. It cannot be differentiated from other forms of bronchopneumonia, and thus infectious etiologies should be excluded by appropriate studies. Clinically, patients present with fever, severe dyspnea, tachypnea, and hypoxemia. Chest radiographs reveal patchy alveolar infiltrates, usually basilar in location. Mortality is as high as 50%. Transbronchial brushings with biopsies and bronchoalveolar lavage may help distinguish infections from acute immunologically mediated pneumonitis. High frequency of anti-SSA/SSB antibodies has been associated with ALP. Given the poor prognosis, therapy requires high-dose corticosteroids (1 to 2 mg per kg per day) or pulse IV methylprednisolone (1,000 mg IV daily for 3 days) along with broad-spectrum antibiotics until final cultures return. Case reports suggest the use of IVCY, plasmapheresis, or immunoglobulins in patients who respond poorly to steroids.

Pulmonary hemorrhage is a rare but potentially fatal complication. Patients characteristically present with acute dyspnea, tachycardia, severe hypoxemia, rales, sudden drop in hematocrit, and hemoptysis. Rarely, diagnosis is delayed due to the absence of hemoptysis. BAL provides the most reliable confirmation with the presence of bloody fluid, hemosiderin-laden macrophages, purulent sputum, and absence of pathogenic organisms on culture and Gram stain. Pathologic findings include intra-alveolar hemorrhage sometimes associated with interstitial pneumonitis or capillaritis. Immunopathologic studies may reveal granular deposition of immunoglobulin G (IgG) in alveolar septal walls and pulmonary vessels, thus suggesting a possible immune complex–mediated process. Therapy is generally aggressive with IV methylprednisolone at 1,000 mg daily for 3 days followed by tapering high-dose oral (1 mg per kg per day) corticosteroids. The addition of IVCY should be considered in patients who are critically ill or fail pulse corticosteroids. Plasmapheresis has been added in case reports, but whether it offers any additional benefit is unclear. Mortality remains high at 80% despite such treatment. (See Chapter 53 for an in-depth discussion of intrapulmonary hemorrhage and pulmonary-renal syndromes.)

The prevalence of ILD is less than 3% in several studies and may occur before or after ALP. Patients usually present with dyspnea on exertion, productive cough, pleuritis, and rales. Pulmonary function tests reveal a restrictive pattern and marked reduction in diffusing capacity. High-resolution thin-section CT may differentiate earlier-stage alveolitis from end-stage fibrosis. The presence of dense alveolar opacities or "ground-glass" appearance suggests active inflammation and may guide therapy. Treatment for ILD is challenging, and there are no prospective randomized trials. Therapy for symptomatic disease begins with high-dose corticosteroid therapy and again, IVCY or AZA has been used in clinically progressive ILD.

Pulmonary arterial hypertension (PAH) in SLE is less common in SLE than other connective tissue diseases and is estimated at 0.9% [43]. Pathologically, changes of intimal thickening and fibrosis, medial hypertrophy, altered elastic laminae, and periadventitial fibrosis have been similar to changes seen in idiopathic pulmonary hypertension. Necrotizing arteritis has been reported. Patients usually present with severe dyspnea on exertion and fatigue. Patients with PAH have a greater frequency of Raynaud's phenomenon than SLE patients without PAH (75% vs. 25%) [44]. In addition, the prevalence of APAs is higher in SLE-associated PAH than in other connective tissue diseases with PAH (47% vs. 19%) [45]. Because symptoms often develop late in the clinical course, assessment with Doppler

echocardiography is useful to monitor for progressive disease requiring therapy.

Therapy for primary pulmonary hypertension is evolving rapidly with the use of IV prostacyclin (epoprostenol), a prostacyclin analog (iloprost), and endothelin-receptor antagonist (bosentan). IV prostacyclin has provided significant benefit in idiopathic PAH, and these therapies have been applied to PAH secondary to systemic sclerosis and less so SLE (also see the section Systemic Sclerosis). Sildenafil (a phosphodiesterase isoenzyme 5 inhibitor that enhances endothelial nitric oxide and cyclic GMP, resulting in selective pulmonary, bronchial, and coronary artery vasodilation) is effective for lupus-related PAH [46]. Calcium channel blockers are ineffective. A retrospective, open-labeled study compared the use of IVCY alone versus IVCY with vasodilator therapy in patients with SLE-related PAH. The patients given IVCY alone had less severe PAH (New York Heart Association, Class II/III) and 50% responded [47]. It is postulated that there may be a role of immune or inflammatory mechanisms in PAH associated with connective tissue disorders. This is an intriguing but yet not proven pathogenesis.

Pulmonary embolism and peripheral vasoocclusive disease are well-known risks in SLE. One prospective study documented the risk of deep vein thrombophlebitis at approximately 12%, with a 9% risk for pulmonary embolism. The risk of thromboembolic events is increased in patients with LAC and APAs (see "Antiphospholipid Syndrome" section).

Other rare pulmonary syndromes occur in SLE. Dyspnea from shrinking lung syndrome can be either acute or chronic and has a prevalence of 0.9% [42]. Postulated mechanisms include myopathy of respiratory skeletal muscles or diaphragm, phrenic neuropathy, or pleural inflammation. Pulmonary function tests reveal reduced total lung volumes with a restrictive pattern while chest radiographs reveal low lung volumes. Acute reversible hypoxemia, possibly secondary to pulmonary leukocyte aggregation, has been described in acutely ill SLE patients. Patients present with severe hypoxemia, hypocapnia, and increased alveolar-arterial PO_2 gradient without obvious parenchymal lung disease. Treatment with high dose glucocorticoids improves oxygenation. Cricoarytenoid or laryngeal involvement causing upper airway obstruction varies from 0.3% to 30% [42]. Bronchiectasis is common but usually clinically asymptomatic.

Cardiac Disease

Cardiovascular involvement in SLE ranges from 29% to 66%. This tremendous range reflects whether data is based on clinical parameters or pathologic findings at autopsy. Often, the latter studies document significant findings in the heart without clinical correlation. However, a multisite international SLE cohort study confirmed that circulatory disease (including cardiac, arterial, and cerebral vascular disease) is the major cause of mortality [48].

Pericardial disease is by far the most common cardiac manifestation of SLE (see Chapter 35) but less common than lupus pleuritis. Subclinical pericarditis is often documented only at autopsy. Pericarditis usually presents in association with other organ system activity, rather than as an initial manifestation of SLE. Classic symptoms include an anterior or substernal pleuritic chest pain that is characteristically relieved by leaning forward. A pericardial rub may be heard. Although objective radiographic, electrocardiogram (ECG), and echocardiographic findings of pericarditis are similar to idiopathic pericarditis, some patients may have relatively normal findings.

Life-threatening complications of pericarditis include cardiac tamponade and constriction. Both entities are rare; the incidence of tamponade is reported at 1% to 2.5% while constriction is described in case reports [49]. Since hemodynamically significant pericarditis is rare, pericardiocentesis fluid data are limited. Typically, pericardial fluid is exudative with high protein and normal-to-low glucose, compared with serum. The total WBC counts from various reports have ranged from 544 to 199,600 cells per μL, with predominantly PMN cells. Thus, suppurative pericarditis becomes a significant and important differential in SLE patients with pericarditis. Other reported pericardial fluid features include low or absent complement levels, lupus erythematosus (LE) cells on Wright stains, and positive ANA titers, but none of these findings can differentiate infectious from lupus pericarditis. Constrictive pericarditis may develop after successful treatment of pericarditis with or without corticosteroids.

Once other causes of pericarditis, including uremia, drugs, or viral infections, have been eliminated, hemodynamically stable but symptomatic pericarditis can be successfully treated with NSAIDs or, occasionally, moderate dose (15 to 30 mg per day) oral corticosteroids. If fever is present and the etiology of the pericardial effusion is not clear, a diagnostic pericardiocentesis may be necessary to rule out bacterial or opportunistic infections. Hemodynamically compromising effusions require pericardiocentesis and high-dose IV corticosteroids (e.g., equivalent of 1 mg per kg per day of prednisone). IVIg has been used for the treatment of life-threatening pericarditis. If effusions recur despite the use of high-dose steroids, repeat drainage, pericardial window, or even pericardial stripping may be required.

Another common cardiac manifestation of SLE is valvular heart disease involving the mitral, aortic, or tricuspid valves, often asymptomatic and picked up on echocardiography. Thickened leaflets are common findings but nonbacterial, verrucous lesions (Libman-Sacks endocarditis) may result in embolic events, secondary infectious endocarditis, or valvular insufficiency or stenosis. At autopsy, 15% to 60% of SLE patients have lesions composed of immune complexes, fibrin, platelets, and fibrotic changes on the ventricular surface of the mitral valve (and less commonly, aortic valve), ventricular endocardium, chordae tendineae, and papillary muscle. Clinically, the presence of these lesions does not correlate with murmurs. Prevalence varies from 11% by transthoracic echocardiogram to 43% by transesophageal approach [50]. If significant valvular dysfunction occurs, valve repair or replacement may be required, but complications include rapid calcification of the repaired valve or bioprosthesis. Ongoing anticoagulation is recommended in some cases.

Since the mid-1980s, the presence of Libman-Sacks endocarditis has been associated with the presence of APAs in SLE and primary antiphospholipid syndrome (APS). However, other studies have not confirmed this association in all patients. Whether valvular lesions associated with APA are different in morphology and location remains unclear. Lifelong anticoagulation is indicated if thromboembolic events occur.

Myocardial involvement in SLE is the least frequent manifestation of cardiac disease and should be categorized as primary or secondary. Primary myocarditis is rare, clinically occurring in 2.1% to 14.0% of SLE patients [51]. M*yocarditis* has been defined as unexplained tachycardia, congestive heart failure, ventricular arrhythmias, conduction defects, ST- or T-wave changes, or cardiomegaly without evidence of valvular or pericardial disease. Congestive heart failure from myocarditis is rare and is estimated to occur in 4% of cases. In most studies cardiac function was evaluated by echocardiography, thallium stress tests, and, rarely, invasive hemodynamic studies. Secondary myocardial dysfunction in SLE includes systemic hypertension, valvular disease, pulmonary disease, coronary artery ischemia (see following discussion), drug toxicity, and amyloidosis. These secondary causes are often more important than true lupus myocarditis. Management of patients with evidence of carditis rests on distinguishing primary from secondary

disorders. In the rare patient who does have myocarditis from SLE, high-dose corticosteroids are indicated. Data regarding the use of immunosuppressive agents is scarce.

Primary coronary artery involvement in SLE includes embolic events, thromboses, or a true vasculitis of the vessels as opposed to secondary changes of premature atherosclerosis. Coronary arteritis is rare and difficult to distinguish from atherosclerosis on arteriographic studies unless repetitive studies are performed. In a prospective study of 100 SLE patients, 5% of those with clinical ischemic symptoms responded to increases in steroid dosage, suggesting active arteritis [51]. This can occur in the absence of extracardiac SLE activity. Thrombosis associated with APAs may contribute to myocardial ischemia.

Myocardial infarction from accelerated atherosclerosis, however, occurs more frequently in SLE patients and especially in the age group between 35 to 44 years. Circulatory diseases including heart disease, arterial disease, and cerebral vascular events is the major cause of death in a large multinational SLE cohort, with a standardized mortality ratio (ratio of deaths observed to deaths expected) of 1.7 [48]. SLE patients in the Nurses' Health Study had a more than twofold age adjusted relative risk for cardiovascular disease [52]. Another large lupus cohort reports 9% to 10% incidence of atherosclerotic disease [53]. The mean age of these patients was 48 years, and lupus was quiescent at the time of angina or myocardial infarction. Subclinical atherosclerotic disease is estimated at 37% to 43% of SLE patients based on arterial calcifications by ultrasound or electronic beam CT. Traditional risk factors are more prevalent in the SLE population but SLE is also an additional major risk. Other identified factors include hyperlipidemia, older age at SLE onset, duration of SLE, hypertension, and duration of corticosteroid use.

The management of SLE patients with acute myocardial ischemia initially should be similar to any patient with atherosclerotic coronary artery disease. However, the etiology of the ischemia must be determined since management of coronary arteritis differs from management of atherosclerotic disease. Evidence of extracardiac SLE activity may be helpful. Laboratory tests, including ANA, anti-dsDNA, complement levels, complete blood count with differential and platelet counts may provide some indicators of SLE activity. LAC and APAs should be checked. ECG, echocardiogram, and thallium stress tests do not distinguish arteritis from atherosclerosis. Coronary arteriogram may be helpful in separating thrombosis and vasculitis from atherosclerosis. However, arteriographic distinction of the latter two may be difficult. If arteriography reveals thrombosis without evident atherosclerosis and the presence of APAs is documented, therapy should consist of anticoagulation and antiplatelet medications.

Conduction abnormalities and arrhythmias due to SLE are usually clinically insignificant. The incidence of atrioventricular nodal block is estimated at 5%. Sinus tachycardia without underlying pathology (fever, dehydration, congestive heart failure, thyroid disease, drug abuse) may be a subtle manifestation of lupus activity. If acute conduction disease is suspected clinically to be secondary to myocarditis or arteritis, a short trial of corticosteroids could be initiated in the hemodynamically compromised patient.

Hematologic Disease

Hematological abnormalities constitute one of the major criteria for SLE. These include hemolytic anemia, thrombocytopenia, leukopenia, and lymphopenia. Anemia is present in 50% of SLE patients, with anemia of chronic disease being the most common etiology [54]. Other causes of anemia include iron deficiency (from menses, gastrointestinal bleeding, or poor iron absorption), autoimmune hemolytic anemia (AIHA), drug induced (cyclophosphamide or AZA), pure red cell aplasia, and chronic renal insufficiency. Rarely, other syndromes including thrombotic thrombocytopenia purpura and macrophage activation syndrome have been reported in SLE patients who have more than two cell lines affected [55].

Only 8% to 28% of lupus patients develop AIHA sometime during the course of their disease. While 18% to 65% of SLE patients have a positive direct Coombs assay, significant hemolytic anemia develops in only 10% [54]. The presence of warm IgG autoantibodies and complement on the red cell surface is characteristic of SLE AIHA. Clinically, AIHA is accompanied by an elevated reticulocyte count and indirect bilirubin and decreased haptoglobin levels. Severe hemolytic anemia, defined as hemoglobin less than 8 g per dL, is often associated with concomitant seizures, nephritis, serositis, and other cytopenias [56]. In addition, 74% of patients with AIHA will have APAs. Over 75% to 96% of patients with AIHA respond rapidly to high-dose corticosteroids (60 to 100 mg per day prednisone orally or with intravenous methylprednisolone at 1.5 mg per kg per day) [57,58]. Prednisone is tapered slowly after 3 weeks, based on laboratory results. If active hemolysis persists after 3 weeks, other therapeutic modalities include danazol, dapsone, immunosuppressive agents, and splenectomy; however, splenectomy induces permanent remission in fewer than 50% of patients. Combination of high-dose steroids and danazol, 800 to 1,200 mg per day, is an alternative treatment for severe AIHA, with subsequent gradual steroid tapering. One retrospective study of SLE patients treated for AIHA suggests that danazol was most effective in long-term treatment [58,59]. The efficacy of IVIg is short term and not sustained. Uncontrolled trials or case reports with AZA, cyclophosphamide, plasmapheresis, or rituximab have shown therapeutic response.

Leukopenia, defined as a total white blood cell count of less than 4,000 per μL, occurs in 50% to 60% of SLE patients, but associated infectious complications are rare unless CD4 counts are below 200. In the febrile, severely neutropenic patient, granulocyte-stimulating factor has been used. *Lymphopenia*, defined as counts lower than 1,500 per μL, is seen in 84% of SLE patients during active disease.

Thrombocytopenia, or platelet counts lower than 100,000 per μL, is observed in 20% to 40% of SLE patients and is severe (less than 50,000 per μL) in 10% of patients. Idiopathic thrombocytopenic purpura (ITP) may be the initial presentation of SLE. In evaluating any patient with thrombocytopenia, underlying causes including drug toxicities, ineffective thrombopoiesis, congestive splenomegaly, dilutional effects, and abnormal platelet destruction by disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), vasculitis, drug-induced infection, or hematological excluded. The pathologic mechanism is usually antiplatelet antibodies, with resultant splenic sequestration and decreased platelet life span, although there is association with elevated APA as well. A bone marrow biopsy is helpful in distinguishing various forms of thrombocytopenia. SLE-associated ITP is characterized by an increased number of megakaryocytes.

Once TTP, HUS, DIC, and drug toxicities are excluded, therapy of severe SLE-associated ITP (less than 50,000 per μL) is similar to that of idiopathic autoimmune thrombocytopenia. Corticosteroid therapy at 1 mg per kg per day is the recommended initial therapy. Subsequent tapering is guided by platelet counts. Administration of IVIg may result in a rapid increase in platelet counts. Recommended doses range from 0.4 to 1.0 g per day or 6 to 15 mg per kg per day for 4 to 7 days, but success at maintaining platelet counts is variable. Splenectomy is an option for patients who fail medical therapy, although sustained remission is seen in only 64% of patients

after splenectomy [60]; thus, the long-term benefit of splenectomy is still questioned. For refractory disease, danazol, 800 to 1,200 mg per day alone or in conjunction with corticosteroids, has been effective in several studies [58]. Immunosuppressive agents include various combinations of vincristine or vinca-loaded platelets, cyclophosphamide, and AZA. Anecdotal evidence and open case reports suggest that rituximab (RTX) is effective for intractable disease [61].

Lupus anticoagulant (LAC) interferes with the activation of prothrombin activator complex (factors Xa and V, Ca^{2+}, and phospholipid) of the intrinsic and extrinsic pathways. The laboratory findings are markedly prolonged partial thromboplastin time and normal or mildly prolonged prothrombin time that cannot be corrected by mixing with normal plasma. In addition, patients may also have false-positive reactions in the test for syphilis (VDRL). (Please see the section Antiphospholipid Syndrome for clinical details.) Although many SLE patients have both LAC and APA, subsets of patients have only one or the other laboratory abnormality.

Gastrointestinal Disease

The gastrointestinal involvement in SLE is not frequently considered because many gastrointestinal symptoms can be attributed to complications of drug therapy, particularly salicylates, NSAIDs, corticosteroids, hydroxychloroquine, and AZA. SLE-related gastrointestinal disease varies from of 8% to 22% and includes serositis, mesenteric vasculitis or thrombosis, pancreatitis, cholecystitis, inflammatory bowel disease, protein losing enteropathy, intestinal pseudo-obstruction, and pneumatosis intestinalis [62,63].

The most serious but rare (< 1%) gastrointestinal complication of SLE is mesenteric vasculitis or thrombosis with subsequent large or small intestinal ischemia. The severity and extent of involvement vary and symptoms may be chronic or acute in presentation. Intestinal involvement ranges from segmental edema or ulcerations to perforations. Evaluation should include plain films, paracentesis (to rule out perforation or bacterial peritonitis), CT scans, or angiography. Although features of dilated bowel, bowel wall edema or enhancement, or edema of the mesentery or its vessels are nonspecific, multiple vessel involvement, often in the areas of ileum and jejunum, is found in SLE mesenteric vasculitis [64]. However, angiographic results may be normal due to small vessel disease. Direct visualization with endoscopy or colonoscopy may also provide useful information.

Lupus peritonitis is less devastating but often quite dramatic in presentation. Peritoneal fluid may be present, and is usually transudative and sterile with a low cell count. Other causes of ascites must be ruled out, including constrictive pericarditis, nephrotic syndrome, and spontaneous bacterial peritonitis. Pancreatitis attributed to active SLE is rare and more often related to usual causes of pancreatitis in non-SLE patients (e.g., drugs, hepatobiliary infection, alcohol, etc.) [63]. In a recent report, protein losing enteropathy and intestinal pseudo-obstruction were the most common gastrointestinal manifestations in hospitalized SLE patients [62].

Management of the SLE patient with abdominal pain does not differ significantly from that for non-SLE patients. In patients with mild to moderate pain with a chronic course, medications and intercurrent disease should be considered first as the cause of pain and surgical consult obtained. If no etiology is found, peritonitis should be considered and treated with a moderate increase in steroids. In patients who present acutely, supportive care should be started and appropriate laboratory and imaging studies performed. Paracentesis should be done to exclude perforated viscus or infection. A therapeutic trial of high-dose steroids can then be instituted if mesenteric vasculitis is suspected. Rapid (12 to 48 hours) response usually is consistent with vasculitis or peritonitis, although complete response is often delayed; if a patient deteriorates clinically, exploratory laparotomy is necessary. If studies suggest mesenteric vasculitis, IVCY may be necessary along with the corticosteroids.

Drug-Induced Lupus

The syndrome of drug-induced lupus (DIL) should be considered in ICU patients if systemic symptoms of fever, arthralgias, arthritis, pleuropericarditis, or, less commonly, rash develop. Because many ICU patients receive medications that potentially induce SLE (Table 193.4), the diagnosis must be excluded. Although some medications, particularly procainamide, hydralazine, and TNF-α inhibitors, produce positive ANA tests, this does not necessarily imply that drug-induced lupus is present. Symptoms typically develop several months after the institution of the offending medication. Although CNS and renal manifestations are rare, case reports of more atypical drug-induced lupus have been reported. Males and females are equally susceptible. DIL is more common in older patients, except for minocycline related DIL. Laboratory values reveal an elevated ESR, mild leukopenia or thrombocytopenia, and positive ANA; antihistone antibodies are present in 90% of patients; and specific antibodies to dsDNA and Smith (Sm) antigen are uncommon. However, TNF-α inhibitors such as etanercept or infliximab have been associated with anti-dsDNA, anti-Ro, anti-Sm, and antineutrophil cytoplasmic antibodies (ANCA) [65]. Discontinuation of the offending medication results in gradual diminution of symptoms that may last as long as a year. NSAIDs or low-dose steroids may control the symptoms, and in patients with severe organ system involvement, treatment is similar to idiopathic lupus.

Most rheumatologists believe that patients with idiopathic SLE who require hydralazine, procainamide, isoniazid, phenytoin, beta-blockers, or other medication that can potentially induce lupus can take these medications. TNF-α inhibitors, however, are relatively contraindicated in SLE. It is advisable to document the clinical and serologic status of the patient before starting the medication.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is defined by vascular thrombosis or pregnancy complications in the presence of moderate-to-high titer IgG or IgM anticardiolipin antibodies (APAs), lupus anticoagulant (LAC), or high titer anti-β_2 glycoprotein-I antibody, documented at least twice 12 or more weeks apart (Table 193.5). Other features often associated with APS, but not included in the classification criteria, include livedo reticularis, skin ulcers, endocardial disease, thrombocytopenia, Coombs-positive hemolytic anemia, and false-positive tests for syphilis [66]. Primary APS occurs in the absence of other connective tissue disease. When APS is associated with SLE or other connective tissue disorders, it is referred to as *secondary APS*. Patients with *catastrophic APS* (CAPS) present with acute multiorgan failure from occlusive vasculopathy of small vessels in the kidney, lungs, brain, heart, adrenal glands, and liver. Large vessel occlusions have also been reported.

The LAC, APAs, and anti-β_2 glycoprotein-I antibody all bind to negatively charged phospholipids. How these antibodies induce thrombosis remains unknown, but interaction with endothelial cells, coagulation factors, and platelets, and complement activation, all play a role. Thromboses and emboli occur in all vessel sizes and organ systems. Nonthrombotic associations include valvular lesions similar to Libman-Sacks, hemolytic anemia, thrombocytopenia, and livedo reticularis.

TABLE 193.4

MEDICATIONS ASSOCIATED WITH DRUG-RELATED LUPUS

Type	Definite	Possible	Rare[a]
Cardiovascular	Methyldopa Hydralazine Procainamide Quinidine Practolol Diltiazem	Captopril Beta-blockers Hydrochlorothiazide Amiodarone Ticlopidine	Reserpine Minoxidil Chlorthalidone Clonidine HMG CoA inhibitors Spironolactone Disopyramide Prazosin
Anticonvulsants or neurologic medications		Phenytoin Mephenytoin Primidone Carbamazepine Trimethadione	Levodopa Ethosuximide Valproate
Psychiatric	Chlorpromazine	Lithium carbonate	Lamotrigine
Antibiotics	Isoniazid Minocycline	Sulfonamides Nitrofurantoin Rifampin	Streptomycin Tetracycline Penicillin Nalidixic acid Griseofulvin, terbinafine
Endocrine		Methimazole Propylthiouracil, Methylthiouracil Glyburide	Tolazamide
Rheumatic	Penicillamine TNF-α inhibitors	Sulfasalazine	Gold salts Allopurinol *p*-Aminosalicylic acid NSAIDs: tolmetin, ibuprofen, sulindac, diclofenac, tolmetin
Others	Interferon gamma	Danazol, dapsone	Psoralen Quinine Leuprolide acetate Promethazine Timolol eye drops Olsalazine, mesalamine Zafirlukast Interleukin 2 Docetaxel

[a]Rare: usually case reports.

The APS manifestations that most likely require ICU admission are cerebrovascular disease, pulmonary embolism, major abdominal or extremity arterial or venous thrombosis, myocardial infarctions, severe valvular disease (insufficiency or thrombotic valvular vegetations), and intracardiac thrombosis. Renal manifestations of APS include hypertension, proteinuria, acute or subacute renal insufficiency, and end-stage renal failure [67]. The classic renal lesion is thrombotic microangiopathy, but the entire renal vasculature can be affected: renal artery lesions can cause renal artery stenosis, cortical ischemia, and infarct, while thrombosis of the renal vein and inferior vena cava result in nephrotic range proteinuria. Hemodialysis patients with APS are at increased risk of vascular access thrombosis. CAPS, which occurs in less than 1% of APS, is the most serious and devastating subset with multisystem small vessel thromboses occurring within a short time period, usually less than 1 week [68]. Differentiation from TTP and DIC is imperative but sometimes difficult since microangiopathic hemolytic anemia or elevated fibrin split products are sometimes present in CAPS. Precipitating factors include infection, surgery, malignancy, subtherapeutic anticoagulation, and SLE flares. Mortality is high, nearly 48%, with death most often associated with renal, pulmonary, splenic, or adrenal involvement, or underlying SLE [69].

APS patients with *venous* thrombosis are treated with heparin anticoagulation followed by conversion to warfarin with an international normalized ratio (INR) target of 2.0 to 3.0. Lifelong anticoagulation is supported by a high incidence of recurrent thrombosis when warfarin is discontinued. A prospective trial comparing two intensities of warfarin for prophylaxis suggests that moderate dose (INR 2.0 to 3.0) is comparable to high dose (INR 3.1 to 4.0) in preventing further thrombosis and equal in bleeding complications [70]. However, in this study, only 24% of patients had arterial thrombosis and thus controversy still exists as to whether high intensity warfarin (INR 3.1 to 4.0) is necessary for patients with arterial clots. In APS patients with recurrent thrombosis despite therapeutic anticoagulation, treatment options include standard dose warfarin plus an antiplatelet agent, high intensity warfarin, unfractionated heparin, or low-molecular-weight heparin. For CAPS, combination therapy with high-dose corticosteroids, high intensity anticoagulation, and IVIg or plasmapheresis has the

TABLE 193.5

MODIFIED SAPPORO CLASSIFICATION CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME

Clinical criteria
1. Vascular thrombosis involving any size vessel (arterial, venous, or capillary)
2. Pregnancy complications
   a. Three or more sequential spontaneous miscarriages before 10 weeks gestation (without obvious causes)
   b. One or more unexplained death of normal fetus beyond 10 weeks gestation
   c. Preterm delivery of normal fetus < 34 weeks due to preeclampsia, eclampsia, or placental insufficiency

Laboratory criteria (measured at least on two occasions, 12 weeks apart)
1. Moderate-to-high titer IgM or IgG anticardiolipin antibodies by ELISA
2. Lupus anticoagulant defined by guidelines from International Society on Thrombosis and Hemostasis
3. High titer (> 99 percentile) IgM or IgG anti-β_2 glycoprotein-I antibody by ELISA

Diagnosis is based on the presence of one clinical and one laboratory criteria. The laboratory finding should not be less than 12 weeks or more than 5 years apart from the clinical event.

Adapted from Miyakis S, Lockshin MD, Atsumi T, et al: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome. *J Thromb Haemost* 4(2):295–306, 2006.

best survival data [68]. There is no evidence to support anticoagulation as primary prevention in individuals who have antiphospholipid antibodies or LAC without thrombotic manifestations [71].

Other causes of hypercoagulability associated with venous thrombosis include deficiencies of protein C, protein S, plasminogen, and antithrombin III; factor V Leiden; prothrombin mutation and homocystinemia; nephrotic syndrome; and paraneoplastic syndrome. In patients with arterial thromboses, homocystinemia, and other nongenetic causes including cocaine use, valvular heart disease, atrial myxoma, and arterial stenosis should be excluded.

SYSTEMIC SCLEROSIS

SSc, or scleroderma, is an immune-mediated disease characterized by progressive fibrosis of the vasculature and viscera resulting in end-organ damage in the skin, heart, lungs, kidneys, and gastrointestinal tract. There are two subsets of scleroderma: (a) limited cutaneous disease, often associated with the anticentromere antibody and (b) systemic/diffuse disease, associated with the presence of antitopoisomerase 1 (SCL-70) or anti-RNA polymerase. Both subsets have potential end-organ complications that result in ICU admission, including severe digital ischemia from Raynaud's phenomenon, respiratory failure, cardiac dysfunction, or renal insufficiency. The following discussion is limited to these areas.

Severe Raynaud's Phenomenon

Although primary Raynaud's phenomenon (RP) is common in the general population (up to 5%), severe secondary RP associated with connective tissue disease often is more difficult to treat and digital ulceration or gangrene may occur in 25% of SSc patients. Dihydropyridine-type calcium channel blockers, usually nifedipine, reduce the frequency and severity of RP attacks, and are considered first-line therapy [72]. Bosentan, a dual endothelin receptor antagonist, is effective in reducing the number of new digital ulcers [73,74]. Limited evidence suggests that sildenafil, a phosphodiesterase inhibitor, reduces the frequency and severity of attacks and promotes healing of digital ulcers [75,76]. Topical nitrates, ACE inhibitors, and α-adrenergic receptor blockade are additional therapies with modest benefit. Intravenous prostacyclin (epoprostenol) or iloprost (a prostacyclin analog) are effective in patients with severe digital ischemia refractory to other therapies (Table 193.6) [77]. Oral prostanoids are less effective. Use of intravenous prostaglandins should be avoided in patients with pulmonary hypertension unless closely monitored. Chemical sympathectomy with lidocaine provides short-term pain relief, but surgical digital sympathectomy is a last alternative when medical therapies fail.

Pulmonary Disease

Pulmonary involvement in SSc is now the major cause of death (more than 50%). The prevalence of lung disease ranges from 25% to 90% [78]. Clinically significant disease from interstitial fibrosis or pulmonary arterial hypertension (PAH) is estimated at 40% (see Table 193.1).

Exertional dyspnea, cough, and basilar crackles are the predominant clinical features of ILD. Radiographs may reveal pulmonary fibrosis in 33% to 40%, with a characteristic basilar reticulonodular or honeycombing pattern [78]. High-resolution CT scans (HCRT) are more sensitive in documenting the reticular and ground glass opacities of ILD when plain radiographs are relatively normal. Pulmonary function tests may reveal abnormalities even before radiographic or clinical findings. The classic pattern is restrictive, with decreased total lung capacity and forced vital capacity. These findings correlate with fibrosis of the chest wall, diaphragm, and pleura. A decrease in diffusing capacity (D_LCO) may occur in either ILD or pulmonary hypertension and has been reported in isolation without other pulmonary function test abnormalities. Patients with ILD may develop secondary PAH, but the degree of PAH is disproportionate to the degree of ILD.

Prevention of progressive fibrotic disease is the goal of treatment for SSc-associated ILD. In one study, the extent of disease on CT was predictive of mortality and FVC decline, suggesting that patients with more advanced CT abnormalities should be treated [79]. Patients with less extensive disease should be monitored closely and treated if there is evidence of radiographic progression or decline in pulmonary function. BAL cellularity does not predict disease progression or response to treatment, and currently has a limited role in the evaluation of ILD, but is useful to rule out infection [80]. A randomized, placebo controlled study of oral cyclophosphamide (1 mg per kg per day titrated to maximum of 2 mg per kg per day) found small but statistically significant improvement in forced vital capacity (FVC), skin score, and subjective symptoms [81]. Another randomized, placebo controlled study of IVCY (0.5 to 0.7 g per M^2 monthly) demonstrated improvement in FVC [82]. Although there are no controlled trials to compare efficacy of oral versus intravenous CY, the IV route is most practical initially in the critically ill ICU patient. Debate exists as to whether concomitant high-dose prednisone or prednisolone provides additional benefit. Case reports and small open studies of mycophenolate mofetil are encouraging, but larger studies are needed.

Isolated PAH is more common in limited scleroderma, but also occurs in patients with diffuse disease, with a prevalence of 12% to 15% [83]. Pulmonary vasospasm and

TABLE 193.6

DRUG THERAPY FOR SEVERE RAYNAUD'S AND PULMONARY HYPERTENSION IN SSC

Drug	Route of administration	Pulmonary arterial hypertension[a]	Severe digital ischemia[a]	Side effects
Epoprostenol	Continuous, intravenous	2 ng/kg/min titrated to 11 ng/kg/min [90]	2 ng/kg/min titrated up to 4–8 ng/kg/min over 5 d [77]	Catheter related; flushing, nausea, jaw pain, diarrhea, depression
Iloprost	Inhalant	5 µg 6–9 times/d [116]	Ineffective	Flushing, jaw pain, ? syncope
Iloprost[b]	Intravenous		0.5–2 ng/kg/d for 6 h for over 3–5 d [117]	Infusion site pain, headache, nausea, diarrhea, vomiting, jaw pain
Treprostinil	Continuous infusion, or subcutaneous	2 ng/kg/min titrated up to 40 ng/kg/min [118]	2 ng/kg/min titrated up to 40 ng/kg/min (case reports)	Jaw pain, headache, diarrhea, nausea, infusion site pain
Treprostinil	Inhalant	6–18 µg 4 times/d		
Bosentan	Oral	125 mg b.i.d. [84,85]	62.5 mg b.i.d. then increased to 125 mg b.i.d. [73,74]	Hepatotoxicity, anemia, edema, male infertility, teratogenicity
Ambrisentan	Oral	5–10 mg/d [86]		Hepatotoxicity, anemia, edema, male infertility, teratogenicity
Sitaxsentan[b]	Oral	100 mg/d [87,88]		Hepatotoxicity, anemia, edema, male infertility, teratogenicity
Sildenafil	Oral	20 mg t.i.d. to 80 mg t.i.d. [89]	50 mg b.i.d. [75,76]	Headache, diarrhea, dyspepsia, flushing

[a]Numbers in brackets are reference numbers.
[b]Not currently available in the United States.

endothelial cell activation with subsequent arterial wall proliferative changes contribute to the development of PAH. Symptoms include exertional dyspnea, fatigue, reduced exercise tolerance, chest pain, syncope, and lower extremity edema, but patients may be asymptomatic until the disease is advanced. The most sensitive tests are decreased diffusing capacity, often with preserved lung volumes, and Doppler echocardiography showing increased pulmonary pressures and right atrial and ventricular hypertrophy. Right heart catheterization is the gold standard for confirmation of suspected PAH and allows vasodilator trials to assess the degree of pulmonary vascular responsiveness to iloprost or epoprostenol, inhaled nitric oxide, or adenosine. General measures include the use of supplemental oxygen for hypoxic patients, diuretics for management of volume overload, and digoxin for atrial arrhythmias. Anticoagulation is recommended for advanced PAH, but controlled studies have not been done.

Treatment for PAH has recently advanced with oral agents in addition to intravenous or subcutaneous prostacyclin (epoprostenol, iloprost, and treprostinil). Bosentan, a dual endothelin receptor A and B antagonist, maintains vasodilation in the pulmonary arterial bed and clearance of endothelin, improves exercise tolerance, reduces symptoms, and stabilizes hemodynamics [84,85]. Bosentan is currently approved by the FDA for treatment of New York Heart Association (NYHA) class II, III, and IV PAH. Ambrisentan, a selective endothelin-A receptor antagonist, recently has been approved for treatment of NYHA Class II and III PAH [86]. Sitaxsentan is another selective endothelin-A antagonist only approved in Europe [87,88]. Sildenafil, a phosphodiesterase-5 inhibitor, increases vascular smooth muscle cyclic guanosine monophosphate (cGMP) with subsequent vasodilation, improves hemodynamic measures, and improves exercise capacity at doses of 20 mg to 80 mg three times a day [89]. Since these oral agents cause fewer side effects and eliminate the need for intravenous or subcutaneous delivery, they now are the preferred initial drugs of choice for treatment of PAH. Intravenous prostacyclin, epoprostenol, and a subcutaneous prostacyclin analog, treprostinil, are approved for treatment of NYHA class III and IV PAH, and epoprostenol has approval for use in SSc PAH [90]. Given the problems associated with the need for continuous delivery and the associated adverse effects, both agents are reserved for patients who have failed oral therapy. Inhaled prostacyclin, iloprost, 2.5 to 5.0 µg dosed six to nine times per day, also has been approved for the treatment of NYHA class III and IV PAH. Combination therapy with inhaled iloprost, intravenous or subcutaneous prostacyclin, and oral agents may provide even greater benefit, but controlled studies are not available. Table 193.6 summarizes the current therapies available for treatment of PAH.

Surgical interventions include atrial septostomy or transplantation. The former is viewed as a bridge to transplantation since it creates a right-to-left shunt to reduce right heart pressures. However, with recent advances in medical therapy, time to transplantation has been prolonged in the PAH population.

Cardiac Disease

Cardiac involvement in SSc may be a primary process within the heart or secondary to other major organ involvement (i.e., pulmonary, renal, vascular, thyroid). Primary cardiac disease in SSc includes pericardial disease, myocardial disease, conduction abnormalities, and arrhythmias. Because the most common symptoms are dyspnea, orthopnea, atypical chest pain, palpitations, fatigue, and dizziness, the clinical manifestations of cardiac disease can be confused with those of other organ systemic involvement. Recent studies have also shown an increased burden of atherosclerotic coronary disease in SSc [91].

Pericardial disease is the most common cardiac manifestation, and as in SLE, asymptomatic pericardial disease based on autopsy series or echocardiographic data has a much higher prevalence than symptomatic disease (33% to 71% vs. 7% to 20%). Pericardial effusions are usually small and do not

influence prognosis. Larger effusions (> 200 mL), however, are associated with poor prognosis. Pericardial tamponade with hemodynamic compromise is rare. Pericardiocentesis is rarely required unless the patient is hemodynamically compromised or febrile and an infectious etiology must be excluded. Pericardial fluid tends to be serous with a wide range of leukocyte counts and with normal complement levels. Corticosteroids are rarely required for treatment.

Myocardial involvement is the most common cardiac finding in patients with SSc at autopsy, ranging from 12% to 89%; however, symptomatic disease occurs less frequently than pericarditis. Pathologically, the most common findings are patchy, focal myocardial fibrosis equally distributed in both ventricles and all three layers of the heart [92]. Autonomic cardiac neuropathy may also contribute to cardiac morbidity in SSc patients.

Clinically, myocardial disease may result in cardiomyopathy, left ventricular diastolic dysfunction, congestive heart failure, angina, conduction abnormalities, or malignant arrhythmias. A high percentage of SSc patients without cardiac symptoms have an abnormal resting ECG, chest radiograph, Holter monitor, or echocardiogram. Electrophysiological studies reveal a high incidence of reentrant supraventricular tachyarrhythmias and atrioventricular conduction delays. Ventricular tachycardia occurs in 10% to 13% of patients and may be the cause of sudden death. Advanced myocardial fibrosis, rather than selective fibrosis of the conduction system, appears to be responsible for conduction abnormalities and arrhythmias.

Evaluation of acutely ill SSc patients for suspected heart disease should include a routine ECG and chest radiograph. Doppler echocardiography provides information regarding the pericardium, valvular function, systolic and diastolic ventricular function, chamber size, wall thickness, and the presence of pulmonary hypertension. Nuclear scanning may reveal subclinical myocardial disease; cardiac catheterization is useful for accurate assessment of pulmonary arterial pressures but is otherwise unremarkable unless the patient has arteriosclerosis. Negative endoyocardial biopsies cannot exclude myocardial fibrosis since the pathologic process tends to be patchy.

Treatment of SSc cardiac disease is tailored to the specific syndrome. Pericarditis can be treated with NSAIDs or low-dose corticosteroids. Diuresis should be pursued with caution in patients with large pericardial effusions. Renal failure has been reported in patients after vigorous diuresis, presumably secondary to hypovolemia superimposed on low cardiac output resulting in decreased renal cortical blood flow. Congestive heart failure is treated as outlined in Chapter 33. However, if echocardiography reveals evidence of diastolic dysfunction, ACE inhibitors or calcium channel blockers may be more appropriate than inotropic agents. A high index of suspicion for coronary artery disease and aggressive management of modifiable risk factors are important aspects of therapy for all patients.

Renal Disease

In addition to cardiac and pulmonary involvement in diffuse scleroderma, significant morbidity and mortality result from renal disease. The onset of accelerated to malignant hypertension accompanied by signs of microangiopathic hemolytic anemia, hyperreninemia, and rapidly progressive renal failure describes a syndrome referred to as *scleroderma renal crisis* (SRC). SRC may develop in up to 15% to 20% of patients with diffuse scleroderma [93]. SRC typically occurs early in the course of disease in patients with diffuse disease, often in the setting of other organ system involvement. Predictors for development of SRC include high skin score, large joint contractures (wrists, elbows, knees), enlarged cardiac silhouette, and prednisone use [93].

Although the pathophysiology of SRC is unknown, several factors contribute to its evolution. The primary event is endothelial cell injury, leading to intimal proliferation and luminal narrowing. Combined with other contributing factors such as vasospasm, decreased renal blood flow leads to increased renin release and clinical development of malignant hypertension and SRC. Moderate-to-high dose corticosteroid use is associated with the development of SRC, possibly because of the inhibition of prostacyclin production. Microangiopathic hemolytic anemia and thrombocytopenia develop with associated elevation of fibrin degradation products, decreased haptoglobin, elevated reticulocyte count, and the presence of urinary hemosiderin. The urinary sediment contains small amounts of protein (< 2.5 g per 24 hours) but typically no red blood cell casts.

The diagnosis of SRC should be strongly considered in the SSc patient with accelerated hypertension. Symptoms of malignant hypertension include headache, confusion, altered vision, and seizures. However, SRC may occur rarely in normotensive patients. Examination of peripheral blood smears for microangiopathy rapidly confirms the syndrome of SRC in a hypertensive patient. Virtually all patients with SRC have elevated plasma renin activity, although serial tests of renin levels in patients with scleroderma are not predictive of the onset of this syndrome.

Since the advent of aggressive management with ACE inhibitors, conservation or improvement in renal function is possible. It is now clear that this class of drugs is the standard of care in SRC. Short-acting ACE inhibitors should be started and titrated upward every 6 to 12 hours. Blood pressure should be controlled within 48 hours. Additional antihypertensives, including calcium channel blockers, can be added. In many patients treated with ACE inhibitors, there may be a transient reduction in glomerular filtration rate and a rise in serum creatinine. In a large prospective observational study of patients with SRC who were treated with ACE inhibitors, 61% had good outcomes (defined as no or temporary dialysis) and only 4% progressed to renal failure or dialysis [94]. In patients with good outcomes after the initial renal crisis, continuing ACE inhibitors indefinitely may provide further benefit to maintain renal function. Survival data of patients with good outcomes after SRC are similar to those of SSc patients without renal crisis. SRC accounts for only 8% of deaths in SSc, but in a retrospective review of SSc patients, those patients with SRC had a long-term survival of only 50% [93]. There is no evidence to support the use of ACE inhibitors for primary prevention of SRC.

Gastrointestinal Disease

Gastrointestinal tract involvement is common in SSc, affecting 50% to 80% of patients. The most common physiologic abnormalities, esophageal dysmotility and decreased lower esophageal sphincter (LES) pressure, are manifested by symptoms of dysphagia and heartburn, respectively. Pathologically, impaired microvascular perfusion initially alters myoelectrical function of the smooth muscle layer and later, hypoperfusion results in fibrotic changes in muscularis, submucosa, and lamina propria [95]. Although dysphagia and heartburn can be treated symptomatically, serious complications include strictures and Barrett's esophagus.

Gastric involvement is less common but can include gastroparesis with symptoms of early satiety, bloating, and vomiting. Telangiectasias are a common source of gastrointestinal blood loss, and gastric antral vascular ectasia (GAVE) may present with acute bleeding and antedate the diagnosis of SSc.

However, other causes of gastrointestinal bleeding also must be excluded.

Small and large intestinal involvement usually occurs concomitantly and results in malabsorption with symptoms of bloating, cramping, and intermittent or severe diarrhea. Hypomotility due to progressive smooth muscle atrophy and fibrosis results in bacterial overgrowth. In addition, adynamic ileus or pseudo-obstruction may occur. Although barium studies reveal wide-mouth sacculations or diverticula on the antimesenteric border, most patients have relatively few symptoms. Fecal incontinence and constipation are common but underreported. Rare complications include obstruction due to fecal impaction, megacolon, and volvulus. Pneumatosis cystoides intestinalis (PCI), or intramural air-filled cysts in the small or large intestines, may be found incidentally or cause abdominal pain, diarrhea, or bloody rectal discharge. Rupture of these cysts results in pneumoperitoneum without peritonitis.

Primary biliary cirrhosis is the most common liver disease associated with SSc. Up to 18% of patients with primary biliary cirrhosis have SSc, usually the limited cutaneous form, whereas 8% of all SSc patients have antimitochondrial antibodies. The liver disease most often follows the diagnosis of SSc but can precede it.

Treatment of gastroesophageal dysmotility and reflux includes modifications in eating and high-dose proton pump inhibitors. Treatment for GAVE includes various therapeutic endoscopic procedures such as cautery, sclerotherapy, and laser ablation. Prokinetic agents, including metoclopramide and macrolide antibiotics, have been reported to be useful in treatment of esophageal, gastric, and intestinal disease. Intestinal malabsorption has been treated with antibiotics, low-residue diets, medium-chain triglycerides, fat-soluble vitamins, and total parenteral nutrition. Octreotide improves intestinal peristalsis in pseudo-obstruction, and in combination with erythromycin may have additive benefits [96]. An investigational 5-HT4 receptor agonist, prucalopride, improves symptoms and gut transport in SSc [97]. Prucalopride recently was approved for use in Europe, but is not yet available in the United States. Cisapride, another 5-HT4 receptor agonist, is severely restricted in the US because of concerns regarding severe cardiac arrhythmias. PCI is usually managed conservatively without surgery, but both malabsorption and PCI are poor prognostic indicators [98].

IDIOPATHIC INFLAMMATORY MYOPATHIES

Polymyositis (PM), *dermatomyositis* (DM), and *inclusion body myositis* (IBM), the most common acquired inflammatory myopathies, are characterized by progressive symmetric proximal muscle weakness and elevated muscle enzymes. Each subtype also has unique clinical and histologic features. In both PM and DM, other organ system involvement is common. DM has classic skin findings including a heliotrope rash on the upper eyelids, scaly erythematous patches called Gottron's papules overlying the MCP and PIP joints and the extensor surfaces of the knees and elbows, and erythema typically in a V shape and mantle distribution on the neck and chest. PM and IBM have no skin manifestations. Both PM and DM may have pulmonary, cardiac, or gastrointestinal involvement. IBM differs from PM/DM in many ways including older age at onset, more indolent course with poor response to treatment, more frequent asymmetric and distal muscle involvement, and often only mild creatinine kinase elevation. The diagnosis of PM/DM is based on criteria established by Bohan and Peter [99]: symmetric proximal muscle weakness, typical rash of DM, elevated serum muscle enzymes, myopathic changes on electromyography, and characteristic muscle biopsy abnormalities. Muscle biopsy is usually required to establish the diagnosis and exclude other causes of muscle weakness. The biopsy should be taken from a muscle that is weak on exam, usually the quadriceps or deltoid. Obtaining the biopsy from a muscle contralateral to one with myopathic changes on EMG may improve the diagnostic yield. T2-weighted MRI with fat suppression can also be useful for identifying an actively inflamed muscle for biopsy [100]. A number of myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs) have been identified that correlate with specific clinical presentations and may contribute diagnostic and prognostic information [101,102]. Anti–Mi-2, found in up to 10% of patients with myositis, is associated with classic DM, and is a marker for a more favorable prognosis. Antibodies against a signal recognition particle (SRP) occur in only 5% of myositis patients but are associated with acute, severe myositis with an overall poor prognosis. Table 193.7 summarizes the various clinical and laboratory features of these three idiopathic inflammatory myopathies.

Inflammatory myositis is also associated with other connective tissue diseases (SSc, SLE, mixed connective tissue disease), malignancy, inborn errors of metabolism, lipid storage disease, and mitochondrial myopathies, but these will not be discussed here. Numerous drugs can cause myopathy or myositis that is sometimes difficult to distinguish from inflammatory myositis. These drugs include lipid lowering agents, glucocorticoids, antipsychotics, antimalarials, colchicine, nucleoside reverse transcriptase inhibitors (NRTIs), alcohol, and cocaine. Bacterial infections (*S. aureus*, *Streptococcus pyogenes, Clostridium perfringens, Borrelia burgdorferi*) and viruses (coxsackievirus A and B, echovirus, influenza A and B, adenovirus 2 and 21, hepatitis B and C, and HIV) can cause a myopathy that may be confused with PM or DM. Parasites including trichinosis, toxoplasmosis, cysticercosis, toxocariasis, and amebiasis may all cause myositis. Muscular dystrophies, neuropathic disease, and metabolic/endocrine diseases also need to be excluded in patients with muscle weakness.

PM and DM are primarily disorders of skeletal muscle, but involvement of the pulmonary, cardiac, articular, gastrointestinal, or vascular systems sometimes lead to catastrophic illness requiring support in an ICU. Moreover, organ dysfunction may occur in patients with overlap syndromes. Respiratory failure, cardiac abnormalities, or comorbidities related to immunosuppression are the most common reasons for ICU admission. A complete discussion of the presentation, diagnosis, management, and differential diagnosis is beyond the scope of this chapter but excellent reviews exist [103–105].

Pulmonary Involvement

Lung disease in PM/DM patients is common (20% to 30% of patients; see Table 193.1) and includes (a) respiratory insufficiency due to weakness of intercostal or diaphragmatic muscles; (b) aspiration pneumonia; (c) pneumonia from neither aspiration nor opportunistic infection; and (d) ILD. Pulmonary vasculitis, pleuritis, pulmonary edema, alveolar hemorrhage, secondary pulmonary hypertension, and bronchiolitis obliterans with organizing pneumonia have also been reported but are uncommon. Dyspnea, cough, and chest pain, are the usual symptoms.

Respiratory failure from intercostal muscle weakness or diaphragmatic dysfunction occurs in 7% of PM/DM patients. Thus, pulmonary mechanics (spirometry, inspiratory force) should be evaluated when respiratory symptoms develop. Serial measurements often predict impending respiratory failure that might necessitate intubation and mechanical ventilation. Management of respiratory failure resulting from muscle weakness is supportive (oxygen, mechanical ventilation) and

TABLE 193.7

FEATURES OF IDIOPATHIC INFLAMMATORY MYOPATHIES

	Polymyositis	Dermatomyositis	Inclusion body myositis
Mean age at onset	45	Childhood or 40	65
Sex (M:F)	1:2	1:2	2:1
Mode of onset	Insidious over months	Insidious over months	Insidious over years
Distribution of muscle involvement	Proximal >> distal symmetric	Proximal >> distal symmetric	Variable, may be primarily distal, asymmetric
Dermatologic findings (see text)	No	Yes	No
Raynaud's	Yes	Yes	No
Pulmonary disease	Yes	Yes	No
Cardiac disease	Yes, rare	Yes, rare	No
Arthritis	Yes	Yes	No
Gastrointestinal tract	Yes	Yes	Cricopharyngeal dysfunction
Creatine kinase	Highly elevated	Highly elevated-classic DM Normal-amyopathic DM	Normal or minimally elevated
Electromyogram/nerve conduction studies	Myopathic features	Myopathic features	Myopathic features but also some neurogenic changes
Histopathology	Endomysial CD8 cells, without vascular inflammation	Perivascular infiltrate of B and CD4 cells and late complements (C_{5-9}, membrane attack complex); perifascicular atrophy	Similar to PM but also presence of intracellular lined vacuoles and inclusions; EM with microtubular filaments
Autoantibodies	Jo-1 (20%), U1-RNP (10%), PM-Scl (10%), SRP (< 5%)	Jo-1 (5%); Mi-2 (10%); U1-RNP (5%); PM-Scl (0.5%)	Rare
Malignancy association	Yes (twofold increase)	Yes (sixfold increase)	No
Response to therapy	Good	Good	Poor

DM, dermatomyositis; EM, electron microscopy; PM, polymyositis; RNP, ribonuclear protein; Scl, scleroderma.

accompanied by therapy directed at the underlying myositis (see Chapter 49).

Bronchopneumonia occurs in up to 24% of PM/DM patients. Contributing factors include pharyngeal incompetence and poor airway protection with subsequent aspiration, iatrogenic immunosuppression, and often a weakened cough. Infectious agents include virulent bacteria and opportunistic organisms. Myositis occurring in the setting of acquired immunodeficiency further expands the possible spectrum of infectious agents. Hence, respiratory symptoms should be evaluated aggressively with chest radiographs and routine and specialized microbiologic techniques (culture for bacteria, mycobacteria, fungi, and smears for *Pneumocystis jiroveci*).

The most common type of parenchymal lung disease in PM/DM is ILD with a prevalence of 20% to 60%. Patients develop progressive dyspnea with or without a nonproductive cough and bibasilar rales. Ground glass opacities and reticulonodular infiltrates may be present on HRCT scans. Pulmonary function tests reveal decreased lung volumes and reduced diffusing capacity. Histopathology usually reveals nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP). Patients with Jo-1 and other antiaminoacyl-tRNA synthetase antibodies have a high incidence of ILD, along with prominent arthritis, fever, Raynaud's phenomenon, and dry, cracking skin lesions referred to as *mechanic's hands*. Fulminant ILD has occurred in amyopathic DM without anti-Jo antibodies.

Myocardial Involvement

Cardiac and pulmonary diseases are the main prognostic factors for PM/DM mortality [106]. Up to 70% of patients have cardiac abnormalities on noninvasive testing, but clinically, few are symptomatic. Myocarditis may manifest as heart failure, arrhythmias, cardiac arrest, or myocardial infarction. It is difficult to diagnose since levels of creatine kinase and muscle brain fractions are elevated as a result of skeletal muscle inflammation. Cardiac troponin I is the most specific marker for myocardial involvement. Cardiac imaging techniques (echocardiogram, gallium citrate or indium-labeled antimyosin antibody detection, and scintigraphic studies) are insensitive and nonspecific for detecting myositis. Contrast enhanced cardiac MRI may provide more information, but large-scale evaluation of its sensitivity and specificity is lacking in PM/DM patients. The gold standard of diagnosis requires endomyocardial biopsy but is invasive. Although previous literature suggested an association of anti-SRP antibodies with myocarditis, recent studies contradict this.

The extent to which any cardiac abnormality is iatrogenic or arises as a complication of the disease is unclear. For example, steroid therapy accelerates atherosclerosis and may exacerbate hypertension, diabetes mellitus, and electrolyte disturbances. Similarly, hypoxia from pulmonary involvement contributes to arrhythmias, axis shifts, and strain patterns on ECG.

Other Organ System Involvement

The major gastrointestinal manifestation of inflammatory myopathies is weakness of the upper pharyngeal striated muscles, resulting in dysphonia, dysphagia, and regurgitation of fluids. Smooth muscle involvement of the distal esophagus is rare, and intestinal vasculitis, commonly seen in childhood dermatomyositis, is also uncommon.

Renal failure and its attendant metabolic abnormalities are the result of rhabdomyolysis, myoglobinemia, and subsequent

myoglobinuria. Myoglobinuric renal failure is rare but tends to occur in patients with acute or hyperacute presentations as a result of widespread muscle necrosis and release of sarcoplasmic materials, including myoglobin. Therapy is directed toward the underlying muscle disease while maintaining an adequate urinary output.

Malignancy

The relationship of PM/DM to malignancy has been established by several epidemiologic studies [107]. DM is associated with the highest risk (sixfold increase compared to age and gender-matched population), while PM has a twofold increase. The risk decreases with time but even at 5 years, the risk is still measurable. Identified risk factors include female sex, later age at diagnosis, cutaneous necrosis and leukocytoclastic vasculitis, and capillary damage. Malignancies commonly associated with DM/PM include breast, ovarian, lung, colon, gastric, pancreatic, nasopharyngeal, and non-Hodgkin's lymphoma [103].

Treatment

High-dose corticosteroids are the first-line therapy for PM/DM, although there are no clinical trials to support this approach. Treatment is usually begun with prednisone 1 to 1.5 mg per kg per day for 6 to 8 weeks, then tapered based on clinical response. In more severe cases (dysphagia, alveolitis, myocarditis, or impending respiratory failure from muscle weakness), IV methylprednisolone may be given at a dose of 1,000 mg daily for 3 days followed by the usual high-dose oral corticosteroid regimen. In steroid responsive patients, a steroid-sparing agent (methotrexate, AZA, mycophenolate mofetil, tacrolimus, cyclophosphamide, or cyclosporine) may be added to facilitate steroid tapering, but efficacy is based on small case series or clinical experience as no randomized clinical trials have been done. IVIg is recommended for patients with severe weakness refractory to steroids based on proven efficacy in a randomized, placebo-controlled trial in patients with DM [108]. Therapy for progressive or severe ILD usually requires the use of corticosteroids and cyclophosphamide. Cyclosporine and tacrolimus can be used in refractory cases. A number of case reports suggest that rituximab can be effective for PM/DM resistant to other therapies, and a placebo-controlled trial is underway. There is conflicting data regarding the use of TNF inhibitors; anecdotal reports suggest benefit for some patients with PM/DM, but lack of efficacy and a high frequency of disease flares were reported in one open-label pilot study [109].

Therapy for IBM is more difficult since it responds to steroids poorly and slowly. IVIg and methotrexate have not been effective in double-blind, placebo-controlled trials. Current recommendations include a trial of steroids if muscle biopsies reveal significant inflammation and physical therapy to help maintain strength and function.

DRUGS USED IN RHEUMATIC DISEASE

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are the cornerstone of therapy in patients with rheumatic diseases. Numerous NSAIDs with variable dosing regimens are currently available. In the intensive care setting, however, comorbidities are often present in the acutely ill patient, and thus limit their use. Potential NSAID toxicities (gastrointestinal bleeding, exacerbation of cardiac and renal dysfunction) may far outweigh their benefits. NSAIDs are contraindicated in patients who are anticoagulated, further restricting their use in critically ill patients.

Corticosteroid Therapy

Although NSAIDs are the drugs of choice in the initial treatment of nonseptic inflammatory joint disease, corticosteroids are more effective for the vasculitides and inflammatory, multisystem autoimmune diseases such as SLE. The physiology and mechanism of action of corticosteroids are beyond the scope of this chapter.

Exogenous corticosteroids at a dose equivalent to prednisone 5.0 to 7.5 mg per day inhibit the hypothalamic-pituitary-adrenal axis. Thus, patients who are on corticosteroids chronically require increased stress doses when situations such as surgery, sepsis, trauma, or other serious medical complications occur. Several corticosteroid preparations are available, which differ in potency, half-life, and mineralocorticoid activity. In the ICU, the most commonly used corticosteroids are hydrocortisone, methylprednisolone, and prednisone. There are few indications to use the long-acting corticosteroids, such as dexamethasone, in patients with rheumatic diseases. At physiologic concentrations, corticosteroids are primarily bound by transcortin, but at higher levels, plasma concentrations of albumin-bound and free corticosteroid are increased. In hypoalbuminemic patients, a greater percentage of corticosteroid is free, thus increasing the anti-inflammatory effects and the toxicities. Since corticosteroids are metabolized in the liver, the concomitant administration of drugs that increase hepatic microsomal enzyme activity (phenytoin, barbiturates) also accelerates corticosteroid metabolism.

The dosage and mode of administration of corticosteroids depend on the clinical situation. In rheumatoid arthritis patients without evidence of vasculitis, joint symptoms usually can be controlled with less than 10 mg per day of prednisone. In contrast, a patient with newly diagnosed DM requires high-dose prednisone (1 to 1.5 mg per kg per day) to achieve disease control. The more usual situation in the ICU is the patient with multisystem involvement from SLE or vasculitis. In these patients, high-dose parenteral methylprednisolone can be initiated at 50 to 100 mg per day.

For acutely ill patients who fail conventional high-dose steroids (i.e., 1.0 to 1.5 mg per kg per day), pulse IV methylprednisolone at 1,000 mg per day infused over 60 minutes and repeated daily for 3 consecutive days may be more effective. Pulse IV methylprednisolone may produce minor side effects, such as metallic taste, facial flushing, transient hypertension, and hyperglycemia. More significant (but rare) toxicities include seizures, anaphylaxis, intractable hiccups, arrhythmias, hemiplegia, psychosis, and sudden death. In four reported deaths, patients were receiving furosemide concurrently. Theories on the mechanism of death include an electrolyte imbalance resulting in cardiac arrhythmias, cardiovascular collapse due to hypovolemia and vasodilation, and anaphylaxis. Data are limited on the actual mechanism of action by pulse methylprednisolone in suppressing SLE or vasculitis activity. In addition, the long-term toxicities are unknown. Thus, these factors must be weighed against the patient's clinical status.

High-dose daily corticosteroids are usually continued for 4 to 6 weeks. If disease activity remains controlled, further tapering should be attempted. Switching to alternate-day steroids reduces hypothalamic-pituitary-adrenal axis suppression and reduces or prevents Cushing's syndrome. This regimen, however, does not prevent steroid-induced osteopenia. If the patient does not improve with high-dose or pulse corticosteroids, the addition of other immunosuppressive agents must be considered.

Immunosuppressive Therapy

Immunosuppressive agents were initially used in rheumatic diseases as steroid-sparing agents. However, convincing evidence exists that these agents can produce dramatic improvement or induce remission in many different rheumatic diseases. The most commonly used drugs include methotrexate, AZA, cyclophosphamide, leflunomide, and mycophenolate mofetil. Cytotoxic drugs should be initiated in patients with life-threatening or organ-threatening diseases that have failed to respond to conventional therapy. In addition, the patient should have reversible lesions rather than end-stage disease. Many of the drugs are teratogens contraindicated during pregnancy. Thus, in any patient starting cytotoxic therapy, pregnancy needs to be excluded. Active infection cannot be present at the start of cytotoxic therapy. Patients with a positive PPD require further evaluation and treatment for active versus latent tuberculosis. Once therapy is initiated, laboratory studies need to be monitored carefully.

The dosing of immunosuppressive agents for the different rheumatic diseases has been discussed in previous sections. In the ICU setting, adjustment to conventional dosing may be necessary based on renal or hepatic function since many of these agents are metabolized or excreted through the kidney or liver. Drug interactions such as allopurinol with AZA or trimethoprim with methotrexate are also important considerations.

Mechanism of Action and Metabolism

All immunosuppressive agents interfere with the cell cycle, and the cytotoxic effects occur through inhibition of cell division.

Azathioprine (AZA), a purine analog, prevents biosynthesis of the purine bases, adenine, and guanine. AZA is a prodrug that is metabolized in the liver to 6-mercaptopurine and then, through the enzyme thiopurine S-methyltransferase (TMPT), to its active metabolites. A genetic polymorphism of TMPT results in variable enzyme activity and predicts greater risk of myelosuppression in patients with low or absent levels. TMPT genotype testing is recommended before initiating AZA therapy [110]. Since 45% of the prodrug is renally excreted, the dose should be reduced in patients with renal insufficiency, but specific recommendations are not available. AZA should be avoided, or the dose markedly reduced, in patients taking allopurinol, which interferes with its metabolism by inhibiting xanthine oxidase.

Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase, whose effects also result in reduced purine synthesis and consequent inhibition of T- and B-cell proliferation. The antiproliferative effects of MMF are relatively specific for lymphocytes. Other potential mechanisms of MMF-induced immunosuppression include induction of T lymphocyte apoptosis and inhibition of adhesion molecule expression. Most of the MMF dose (90%) is excreted renally and the remainder by enterohepatic elimination. Dose adjustment is necessary in patients with renal insufficiency.

Methotrexate (MTX) inhibits dihydrofolate reductase, thus reducing intracellular tetrahydrofolate levels and interfering with tetrahydrofolate dependent metabolic pathways, which include purine and pyrimidine metabolism. Potential mechanisms whereby MTX exerts an anti-inflammatory effect include increased extracellular adenosine concentrations, reduction of inflammatory cytokines (IL-1B and IL-6), inhibition of cyclooxygenase and lipoxygenase activity, and induction of apoptosis. MTX and its metabolites are excreted by the kidney. Methotrexate should not be used in patients whose estimated glomerular filtration rate is less than 30 mL per minute.

Leflunomide (LEF) selectively inhibits dihydroorotate dehydrogenase, an enzyme critical in the de novo synthesis of pyrimidine ribonucleosides. By reducing the pyrimidine pool and thus inhibiting DNA synthesis, LEF is postulated to modulate pathogenic T-cell proliferation and the subsequent inflammatory cascade. LEF has a very long half-life, is highly protein bound, undergoes enterohepatic recirculation, and is eliminated by the gastrointestinal tract and kidneys. It should not be used in patients with hepatic or severe renal impairment.

Cyclophosphamide (CY) is an alkylating agent that binds to DNA and prevents cell replication. CY is cytotoxic to both resting and dividing lymphocytes. It globally reduces T-cell function, and reduces B-cell numbers and antibody production. CY is metabolized by the liver to several active and inactive compounds that are also excreted in the urine. Dose adjustment is recommended for patients with renal insufficiency (Table 193.2.) Hepatic impairment does not appear to alter CY clearance. Hepatic and renal function should be monitored.

Toxicities

Toxicities common to all immunosuppressive agents include bone marrow suppression, infections, and gastrointestinal irritation. Bone marrow toxicity may occur anytime, as early as 1 or 2 weeks after institution of therapy. Leukopenia, especially granulocytopenia, is common. Anemia and thrombocytopenia may occur in conjunction with leukopenia but rarely alone. Infections secondary to immunosuppression occur with any drug but do not necessarily correlate with the degree of leukopenia, duration of drug therapy, or concomitant corticosteroid therapy. MTX and LEF are rated as pregnancy class X (contraindicated, risk outweighs benefits), and should not be used during pregnancy. AZA, rated as class D (positive evidence of risk), is considered safer than many other immunosuppressive agents during pregnancy based on literature in the transplant population. When the benefit of immunosuppression appears to outweigh the risks (e.g., in renal transplant recipients, active lupus, or inflammatory bowel disease), AZA is preferred over other immunosuppressive medications. We strongly recommend avoidance of CY and MMF (both pregnancy class D) during pregnancy except in life-threatening medical conditions in which no alternative therapy is available.

Specific toxicities of AZA include hypersensitivity hepatitis characterized by elevated transaminases and cholestasis that usually resolve after drug discontinuation, but irreversible damage has been reported. Pancreatitis has also been associated with AZA. Azoospermia, anovulation, and teratogenesis are unusual. TPMT levels do not predict these toxicities, in contrast to the known association of low enzyme level with risk of myelosuppression. It is uncertain whether neoplasia occurs at a greater incidence in rheumatic patients treated with AZA as compared to transplant patients. However, relative risk of lymphoproliferative disorders in RA patients receiving AZA is estimated at 2.2% to 8.7%.

The toxicity profile of MMF is similar to AZA and includes hepatitic abnormalities and myelosuppression. Gastrointestinal intolerance with nausea, vomiting, and diarrhea may improve over time and seldom requires drug discontinuation. A delayed release formulation is available that may improve GI tolerance. There is some evidence that MMF provides protection against fungal infections. As with other immunosuppressive medications, there may be an increased risk of malignancies, including lymphoma.

MTX's minor toxicities include nausea, vomiting, anorexia, diarrhea, and weight loss. Stomatitis occurs with variable severity. Alopecia, photosensitivity to ultraviolet light, urticaria, and cutaneous vasculitis may occur. Major hematological toxicities include megaloblastic anemia and, rarely, pancytopenia. Elevations in hepatitic enzymes also occur and require careful monitoring. Hepatic fibrosis is an infrequent but concerning complication. Acute interstitial pneumonitis is the most

common pulmonary toxicity associated with MTX. Other pulmonary toxicities include interstitial fibrosis, pleuritis, noncardiogenic pulmonary edema, and increased pulmonary nodulosis. Opportunistic infections, including *P. jiroveci* pneumonia, cryptococcosis, and disseminated herpes zoster, have occurred with low-dose weekly MTX therapy for RA. Small series have reported development of lymphoproliferative disorders in MTX-treated patients, and it is well established that RA patients are at greater risk for lymphoma. However, a study reviewing a national data bank for rheumatic disease in over 18,000 patients did not identify a significantly higher risk of lymphoma in patients treated with MTX [111]. Risk factors for MTX toxicity include renal insufficiency, viral infections, folic acid deficiency, and concurrent use of trimethoprim-sulfamethoxazole and probenecid. For a MTX overdose, folinic acid (leucovorin), in a dose equal to the MTX dose, should be given every 4 to 6 hours until the serum MTX level is no longer detectable.

Toxicities associated with LEF include diarrhea, alopecia, rash, hypertension, and peripheral neuropathy. Liver enzymes may be elevated but usually return to normal with dose reduction or drug discontinuation. In patients who experience severe side effects or who wish to become pregnant, elimination of LEF and its metabolites can be accelerated by the administration of cholestyramine, 8 g three times a day for 11 days.

The major side effects of CY are infertility, bladder toxicity, carcinogenicity, and bone marrow suppression. Oral and IV regimens induce gonadal dysfunction in men and women because of injury to germinal epithelium. Azoospermia in males and amenorrhea in premenopausal women is dose related and is usually permanent. The risk may be reduced by the induction of gonadal quiescence during CY treatment. Leuprolide was shown to preserve ovarian function in women treated with CY for LN [112]. Leuprolide was ineffective in men, but a small study has shown a reduced risk of azoospermia in men treated with testosterone [113]. Sperm banking is also recommended for men undergoing CY therapy. Cryopreservation of ova or embryos is usually not practical as it entails hormonal manipulation and significant delay in treatment. Hemorrhagic cystitis due to acrolein, a metabolite of CY, occurs in 20% to 30% of patients receiving oral CY. Bladder carcinoma occurs in 10% of patients who receive long-term CY therapy, even 20 years after exposure. IVCY may have fewer bladder complications than the oral regimen. Adequate hydration for all patients and concomitant use of sodium 2-mercaptoethane sulfonate (MESNA) during IVCY infusion in patients with renal insufficiency reduce the risk of hemorrhagic cystitis. The regimen is outlined in Table 193.2. Skin and hematologic malignancies and premalignant and malignant changes of the cervix are also associated with CY. Hepatotoxicity is rare, but nausea or vomiting with IVCY is common. Other toxicities include infections, cardiomyopathy, and pulmonary fibrosis. *P. jiroveci* pneumonia has also occurred in patients with autoimmune diseases treated with CY and steroids. PCP prophylaxis is recommended for all patients treated with CY.

Biological Modifiers

In addition to the above traditional immunosuppressive agents, this past decade has witnessed the development of multiple biologic modifiers for the treatment of rheumatic diseases including anticytokine therapies, T-cell costimulation blockade, and B-cell depletion (see Table 193.8). Biologic agents are increasingly used to treat rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Use of biologic agents in other rheumatologic diseases is still in investigational stages. It is unlikely that the ICU physician will initiate any of these agents for therapeutic indications. However, if a patient is receiving one of these agents chronically, it is important for the

TABLE 193.8

BIOLOGIC AGENTS FOR THE TREATMENT OF RHEUMATIC DISEASES

Drug	Mechanism of action	Half-life	Side effects
Etanercept	Soluble p75 TNF-α receptor fusion protein	72–132 h	Injection site/infusion reaction, Tb reactivation, opportunistic infections, fungal and mycobacterial infections, demyelinating syndromes, drug-induced lupus, pancytopenia, aplastic anemia, hepatotoxicity, CHF, possible increased risk of lymphoma and nonmelanoma skin cancer
Infliximab	Chimeric anti-TNF-α monoclonal antibody	7–12 d	
Adalimumab	Human anti-TNF-α monoclonal antibody	10–20 d	
Golimumab	Human anti-TNF-α monoclonal antibody	14 d	
Certolizumab pegol	Human anti-TNF-α antibody Fab' fragment coupled to polyethylene glycol	14 d	
Abatacept	CTLA4-Ig soluble fusion protein, inhibits T-cell activation by blocking costimulatory signal	8–25 d	Infusion reactions, infections, COPD exacerbation, possible increased risk of lung cancer and lymphoma
Tocilizumab	Humanized IgG1 IL-6 receptor antibody	6–13 d	Infusion reactions, infections similar to TNF-α inhibitors, hypertension, hypercholesterolemia, elevated hepatotoxicity gastrointestinal perforation
Anakinra	Human recombinant IL-1 receptor antagonist	4–6 h	Injection site reactions, serious infections
Rituximab	B-cell depleting chimeric monoclonal CD20 antibody	19 d	Infusion reactions, PML, new or reactivated viral infections, including fulminant hepatitis B

TNF, tumor necrosis factor; Tb, tuberculosis; Fab, fragment antigen binding; CTLA4, cytotoxic T lymphocyte-associated antigen; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IL, interleukin; PML, progressive multifocal leukoencephalopathy.

ICU team to understand the mechanism of action and the potential complications or toxicities of these therapies [114].

Five biologic agents that inhibit TNF-α, one IL-6 inhibitor, and one IL-1 receptor antagonist are currently available to treat rheumatoid arthritis (RA). The TNF-α inhibitors are also used to treat psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Because antigen-activated T cells initiate the cell-mediated immune response and the cytokines TNF-α, IL-1, and IL-6 promote the inflammatory processes in inflammatory joint diseases, these anticytokine therapies control signs and symptoms of inflammatory arthritis, and in RA and PsA, have been shown to retard the progression of joint damage.

Four TNF-α inhibitors (etanercept, infliximab, adalimumab, and golimumab) are currently approved in the treatment of moderate-to-severe RA, psoriatic arthritis, and ankylosing spondylitis. Certolizumab pegol, the newest of the TNF-α inhibitors, is currently approved for RA and is being studied for use in other types of inflammatory arthritis. Although TNF-α has many diverse cellular effects in RA and other inflammatory arthropathies, it acts as a potent inflammatory cytokine by binding to one of its receptors, p55 or p75, on chondrocytes, fibroblasts, and osteoclasts in the rheumatoid synovium and stimulates the production of metalloproteinases and other effector molecules that damage the joint. In addition, TNF-α–activated endothelial cells express adhesion molecules, which promote the ingress of PMN cells into the joint. Naturally occurring soluble TNF-α receptors, which theoretically should neutralize TNF-α, exist in high concentrations in rheumatoid synovial fluid but may be inadequate in concentration to neutralize TNF-α in this disease.

Etanercept, a fusion protein comprised of two recombinant p75-soluble TNF-α receptors combined with the Fc portion of human IgG, is administered in subcutaneous injections (25 mg twice a week or 50 mg weekly) alone or in combination with methotrexate. Adalimumab and golimumab are recombinant human IgG_1 monoclonal antibodies against TNF-α. Adalimumab is administered as a 40 mg subcutaneous injection every other week, and golimumab is given in a single monthly 50 mg subcutaneous injection. Infliximab, a chimeric (human and mouse) monoclonal antibody against TNF-α, is administered intravenously at starting doses of 3 mg per kg at weeks 0, 2, and 6, followed by maintenance infusion every 8 weeks. The dose can be titrated to response with maximal dosage of 10 mg per kg. Certolizumab is a human anti-TNF-α antibody Fab' fragment that is chemically linked to polyethylene glycol. Certolizumab is administered by subcutaneous injection at 2- or 4-week intervals. Methotrexate is recommended in combination with infliximab and adalimumab to reduce the frequency of neutralizing human/antichimeric antibodies or human/antihuman antibodies respectively. All five TNF-α inhibitors have been demonstrated in controlled studies to provide clinical benefit and, more importantly, halt the progression of joint damage in RA and PsA.

Short-term toxicities of etanercept, adalimumab, golimumab, and certolizumab include injection site reactions with local urticarial lesions that often resolve with subsequent repeated dosing. Mild hypersensitivity reactions with infliximab infusion occur in 20% of patients, but 2% will experience severe infusion reactions. There is an increased risk of serious infections in patients taking TNF-α inhibitors, including opportunistic, fungal, and mycobacterial infections. All patients should be tested for latent TB prior to initiating therapy with a TNF-α inhibitor and patients with known hepatitis B infection should not receive these drugs.

Demyelinating syndromes have been reported in patients treated with TNF-α inhibitors. Immunogenicity, low-titer anti-dsDNA antibody, and drug-induced lupus syndromes have been documented in patients treated with TNF-α inhibitors. Pancytopenia, aplastic anemia, elevated liver function tests, and exacerbation of preexisting or new onset congestive heart failure have all been reported. Long-term toxicities, including increased risk for malignancy, are an ongoing concern, although the data is inconclusive. Initial surveillance suggested a higher incidence of lymphoma and nonmelanoma skin cancers. Recent meta-analysis of published articles on TNF-α inhibitors suggests a higher rate of malignancy than patients in placebo or methotrexate groups [115]. However, other studies from large patient data bank registries from the United States and Europe have not shown increased malignancy rates associated with TNF-α inhibitors [111].

IL-1, produced by rheumatoid synovial macrophages, acts synergistically with TNF-α on synovial fibroblasts, chondrocytes, endothelial cells, and osteoclasts to promote influx of PMNs into the joint, release of metalloproteinases and collagenases from chondrocytes, and activation of osteoclastic bone resorption. IL-1 binds to two types of cell-surface receptors, but only type I is capable of intracellular activation. Anakinra, a human recombinant IL-1–receptor antagonist, competitively inhibits IL-1 binding to type 1 receptors and is approved for treatment of moderate-to-severe RA. Because of its short half-life, anakinra must be administered daily as a 100 mg subcutaneous injection. Toxicities include injection site reactions and an increase in serious infections. Due to the need for daily injections, modest benefit in RA, and the availability of other biologic agents, anakinra is seldom used for RA, although it remains an effective therapy for some cryopyrin-associated periodic syndromes.

IL-6, a proinflammatory cytokine expressed in RA synovial tissues, promotes the activation of B-cells, T-cells, and macrophages, and upregulation of endothelial adhesion molecule expression. IL-6 also stimulates osteoclast maturation and promotes bone erosion. Tocilizumab, a humanized IgG1 anti-IL-6 receptor antibody, is approved for treatment of RA in patients who fail to respond to DMARDs and TNF-α inhibitors. Tocilizumab is administered as a monthly IV infusion either alone or in combination with weekly methotrexate. The risk of serious infection is similar to the TNF-α inhibitors. TB has been reported, but there is insufficient data to quantify the risk. To date, there is no evidence of an increased incidence of malignancies in RA patients treated with tocilizumab, but long-term data is not available. In clinical trials, tocilizumab has also been associated with hypertension, hypercholesterolemia, elevated liver transaminases, and lower gastrointestinal perforation.

Rituximab (RTX), a chimeric monoclonal antibody to CD20 that results in depletion of mature B cells and disruption of T-cell activation, has been used for treatment of non-Hodgkin lymphoma (NHL). Rituximab is approved for treatment of RA in combination with methotrexate in patients who failed other disease modifying antirheumatic drugs (DMARDs) including anti-TNF-α therapies. Toxicities include infusion reactions with hypotension, fever, and nausea. Serious and potentially fatal viral infections, either new or reactivated, including reactivation of hepatitis B with fulminant hepatitis and hepatic failure, have been reported. There does not appear to be an increased risk of serious bacterial infections in RA patients treated with rituximab, but of the infections reported, respiratory tract infections are the most common. No opportunistic infections or tuberculosis, and no increased risk of malignancy have been reported in the limited follow up of treated RA patients. Data from the NHL database on rituximab has been reassuring in that serious adverse events were infrequent. However, there are case reports of progressive multifocal leukoencephalopathy (PML) in patients with RA and SLE.

Abatacept, a selective modulator of T-cell activation, is approved for the treatment of moderate-to-severe RA in patients who have an inadequate response to methotrexate, other DMARDs, or TNF-α inhibitors. In addition to cognate binding of the T-cell receptor to MHC/antigen on the antigen presenting cell (APC), T-cell activation requires a second costimulatory

TABLE 193.9

MANAGEMENT OF RHEUMATIC DISEASES: AVAILABLE TRIALS AND STRENGTH OF EVIDENCE

	Treatment recommendations	Strength of evidence[a]
Systemic lupus erythematosus (SLE): Lupus nephritis (LN)	Improved long-term preservation of renal function in proliferative glomerulonephritis with CY, AZA, or combination therapy when compared with high doses steroid alone [25]	A
	Combination therapy of IVCY with high-dose methylprednisolone improves renal outcome without significant toxicities [26]	A
	MMF is as effective as IVCY in induction of remission of class III and IV LN without differences in toxicity; MMF more effective than IVCY in patients of Hispanic or African origin [27,28]	A
	Low dose IVCY is equivalent to high dose IVCY efficacy for induction, sustained stabilization, toxicity profile over 10 years in LN (Class III, IV, V) [31]	A
	Short-term induction with IVCY followed by MMF or AZA for maintenance, if better at maintaining remission of lupus glomerulonephritis than long-term IVCY [29]	A
	MMF is equivalent to IVCY in induction of remission of Class V LN [33]	A
SLE: Neuropsychiatric (NSPLE)	IVCY is more effective than pulse methylprednisolone alone for severe NPSLE [39]	A
Antiphospholipid syndrome (APS)	High intensity warfarin therapy is not superior to moderate intensity warfarin therapy in patients with APS [70]	B
	Asymptomatic, persistently APA-positive individuals do not benefit from low-dose aspirin for primary thrombosis prophylaxis [71]	B
Systemic sclerosis (SSc): Raynaud's phenomena (RP)	Intravenous prostanoids are effective in healing digital ulcers in patients with SSc RP [77,117]	A
	Bosentan is effective in preventing new digital ulcers in patients with SSc RP [73,74]	A
	Sildenafil reduces the frequency and severity of attacks and promotes healing of digital ulcers in SSc RP [75,76]	B
SSc: Interstitial lung disease	Both IVCY and oral CY provide modest improvement in SSc lung function, dyspnea, and skin scores compared to placebo [81,82]	A
SSc: Pulmonary hypertension (PAH)	Continuous infusion of epoprostenol for SSc related PAH improves exercise capacity and hemodynamics compared to conventional therapy [90]	B
	Oral bosentan improves exercise capacity, dyspnea index, and functional class when compared with placebo in patients with PAH [84,85]	A
	Sildenafil improves exercise tolerance, functional class, and hemodynamics compared to placebo in patients with PAH [89]	B
	Ambrisentan improves exercise capacity, functional class, and hemodynamics in patients with PAH [86]	B
	Sitaxsentan improves exercise capacity, functional class, and hemodynamics in patients with PAH [87,88]	A

[a] *Strength of Evidence* (based on Ebell MH, Siwek J, Weiss BD, et al: Strength of Recommendation Taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 69:548–556, 2004).
Level A recommendation is based on consistent and good-quality patient-oriented evidence; *Level B* recommendation is based on inconsistent or limited-quality patient oriented evidence.
APA, antiphospholipid antibody; AZA, azathioprine; IVCY, intravenous cyclophosphamide; MMF, mycophenolate mofetil.

signal delivered by binding of the T-cell CD28 receptor to an APC-bound B7 molecule. Abatacept (CTLA4-Ig) is a soluble fusion protein comprised of the extracellular domain of CTLA4 and the Fc portion of IgG1 that interferes with T-cell activation by binding to CD80 (B7-1) or CD86 (B7-2), thereby inhibiting the required costimulatory signal. Toxicities include hypersensitivity infusion reactions, infections, exacerbation of COPD, and potential concerns about malignancies including lymphoma and lung cancer.

An admitted ICU patient who has recently received one of these biologic agents should be approached as an immunocompromised host. Atypical or opportunistic infections are high on the differential if the patient is febrile. In addition, other toxicities of these drugs (although rare), including cytopenias, liver function abnormalities, atypical neurological symptoms, and congestive heart failure, may contribute to the patient's overall medical status. Given the critical nature of the illness that requires ICU care, it is prudent to postpone patients' scheduled doses of these biologic agents until their medical status is more stable. The biologic agents should not be used in patients with active infections. There are no well-controlled studies of the use of these agents in pregnant women. The TNF-α inhibitors and anakinra are rated pregnancy class B (no evidence of risk). Abatacept, rituximab, and tocilizumab are all class C (risk cannot be ruled out). Use of these biologic agents should be avoided during pregnancy unless no alternative therapies are available. Given the limited data on long-term toxicities of biologic therapies, vigilance in surveillance of toxicities is imperative and ongoing.

Advances in management of rheumatologic diseases, based on randomized controlled trials or meta-analyses of such trials, are summarized in Table 193.9.

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CHAPTER 194 ■ ANAPHYLAXIS

FREDERIC F. LITTLE AND HELEN M. HOLLINGSWORTH

Anaphylaxis is the most severe and potentially fatal form of the immediate hypersensitivity reactions. The term *anaphylaxis* (antiphylaxis) is derived from the Greek and means "against protection" [1]. It describes the shock-like state that is caused by contact with a substance and contrasts with the term *prophylaxis*, which denotes a beneficial or protective state resulting from contact with a substance.

The clinical features of anaphylactic reactions are the physiologic sequelae of release of chemical mediators from tissue-based mast cells and circulating basophils and include a potential for life-threatening vascular collapse and respiratory obstruction [2,3]. A clinically and physiologically indistinguishable hypersensitivity reaction, which is called an anaphylactoid reaction, differs from anaphylactic reactions only because the chemical mediators are released by nonimmunologic mechanisms. Since the clinical features are indistinguishable, both will be referred to collectively as anaphylactic reactions [4].

Estimation of the annual incidence of anaphylactic reactions is hampered by complex coding and incomplete reporting. A recent European study estimated annual incidences of severe and fatal anaphylaxis at 1 to 3 per 10,000 and 1 to 3 per million, respectively [5]. Extrapolations from a comprehensive study of emergency department visits in a geographically defined U.S. population predict about 245,000 outpatient episodes of severe anaphylaxis annually. The additional cases consequent to medicines and radiocontrast media in hospitalized patients would at least equal the emergency room number. An estimated 1,500 people die of anaphylaxis per year, stressing the importance of prevention, as well as prompt diagnosis and treatment [6,7].

PATHOPHYSIOLOGY OF ANAPHYLACTIC REACTIONS

Mechanisms of Release of Chemical Mediators

In humans, anaphylaxis involves a series of steps that result in the release of chemical mediators from tissue-based mast cells and circulating basophils. First, contact with an antigen stimulates the generation of antibodies of the immunoglobulin E (IgE) class. Next, the IgE molecules bind by way of their Fc receptor to a glycoprotein receptor on the cell-surface membrane of tissue mast cells and blood-borne basophils, the so-called target cells. As many as 4,000 to 100,000 IgE molecules normally bind to a single target cell, and up to 100,000 to 500,000 in atopic individuals [8,9]. This binding may remain for weeks to months. When two IgE molecules with the same Fab binding (antigen recognition) specificity are in close proximity on the surface of mast cells and basophils, the cells are termed *sensitized*.

For subsequent antigenic exposure to stimulate the release of mediators from mast cells and basophils, the specific antigen must bind to the Fab portion of two IgE molecules fixed to the surface of the target cell. This bridging of two IgE molecules initiates a series of biochemical modifications called the activation–secretion response (Fig. 194.1). This sequence causes secretion of preformed primary mediators of anaphylaxis from cytoplasmic granules in target cells, including histamine, serotonin, eosinophil chemotactic factor of anaphylaxis (ECF-A), heparin, neutrophil chemotactic factor, and proteolytic enzymes that include tryptase [10].

The activation–secretion response also stimulates synthesis of kallikrein [11,12] and newly generated, secondary lipid mediators, which include platelet-activating factor (PAF) [1]; prostaglandin D_2 (PGD_2), a product of the cyclooxygenase pathway of arachidonic acid metabolism [12]; and leukotrienes C_4, D_4, and E_4 (LTC_4, LTD_4, and LTE_4), products of the lipoxygenase pathway of arachidonic acid metabolism. Several cytokines are also released after activation, including interleukins (IL-1, IL-2, IL-3, IL-4, IL-5, and IL-6), tumor necrosis factor, endothelin-1, and granulocyte-macrophage colony stimulating factor [13].

A variety of substances may induce IgE antibody formation and, on subsequent challenge, provoke anaphylactic reactions [14]. The most common substances are drugs, insect venoms, foods, and allergen extracts used in specific immunotherapy (SIT) [15,16]. These and other less common causes of IgE-mediated anaphylaxis are outlined in Table 194.1.

Non–IgE-mediated anaphylaxis occurs when certain ingested or infused substances cause direct mast cell and basophil activation. Clinically significant examples of non–IgE-mediated anaphylaxis are noted in Table 194.2. The administration of blood, serum, or immunoglobulins to patients who are IgA deficient can result in immune complex formation between donor IgA and recipient IgG anti-IgA antibodies [4,17]. These immune complexes fix complement causing activation of the complement cascade with release of the C3a and C5a complement fragments. C3a and C5a are anaphylatoxins and can directly activate mast cells and basophils.

Physiologic Properties of the Chemical Mediators of Anaphylaxis

The most important chemical mediators of anaphylaxis are histamine, cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4), PAF, and bradykinin. Physiologically, these substances increase arteriolar vasodilatation, enhance capillary permeability, recruit other inflammatory cells, and precipitate bronchoconstriction (reviewed in [18]). The contribution of multiple mediators other than histamine explains the limited benefit of antihistamines *alone* in treating anaphylaxis.

Histamine (reviewed in [19]) acts to (a) increase capillary permeability by stimulating terminal arteriolar dilatation and contraction of endothelial cells in postcapillary venules, which opens intercellular gaps, and, as a result, causes the development of urticaria and angioedema; (b) increase secretion from nasal and bronchial mucous glands; (c) stimulate

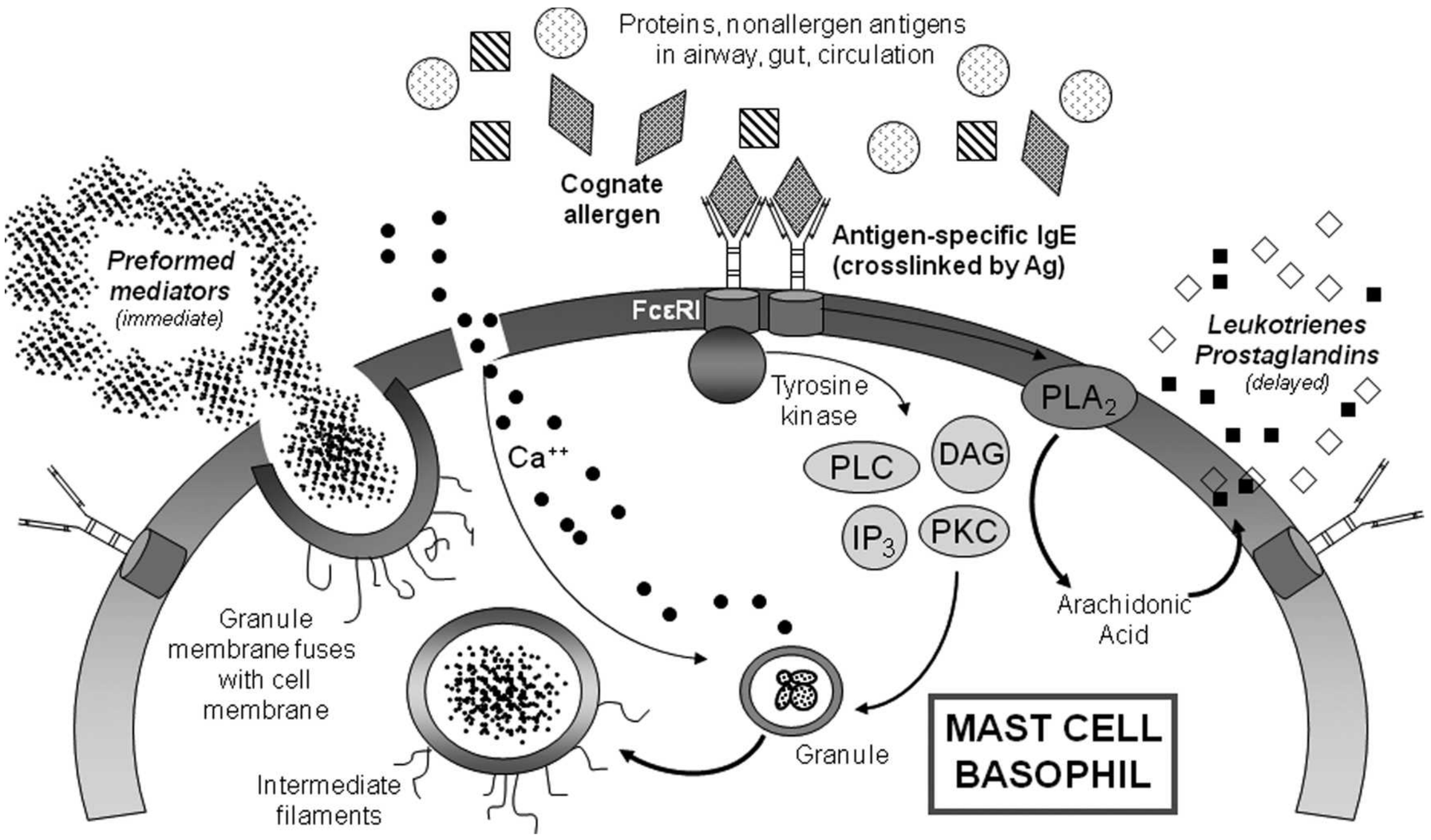

FIGURE 194.1. Chemical mediator release. When two IgE molecules are bridged by an antigen that is specifically recognized by those IgE molecules, a cascade of transmembrane and intracellular events is triggered. The end result is the extrusion of granule contents (mediators) into the extracellular space and elaboration of other, newly formed mediators. Tyrosine kinase appears to be an important intramembrane messenger that initiates the intracellular cascades. At least one cascade involves PLC, which mediates calcium influx into the cell and catalyzes hydrolysis of phosphatidylinositol into the secondary messengers 1,4,5-IP_3 and 1,2-DAG. IP_3 plays a role in calcium mobilization; DAG mediates production of arachidonic acid metabolites and activates PKC. PKC, in turn, participates in the fusion of granules within the cell membrane. PLA_2 mediates the conversion of membrane phospholipid into arachidonic acid, resulting in elaboration of prostaglandins and leukotrienes. Ag, antigen; DAG, diacylglycerol; IgE, immunoglobulin E; IP_3, inositol triphosphate; PKC, protein kinase C; PLA_2, phospholipase A_2; PLC, phospholipase C.

TABLE 194.1

CAUSES OF IMMUNOGLOBULIN E–MEDIATED ANAPHYLAXIS[a]

Type	Agent	Example
Proteins	Allergen extracts	Pollen, dust mite, mold
	Vaccines	Influenza
	Venoms	Hymenoptera
	Heterologous serum	Tetanus antitoxin [16], antithymocyte globulin, snake antivenom
	Others	Heparin, latex [113], thiobarbiturates, seminal fluid
Hormones		Insulin [140], ACTH, TSH [16] progesterone, salmon calcitonin
Haptens	Antibiotics	Beta-lactams [73], ethambutol, nitrofurantoin, sulfonamides [74], streptomycin, vancomycin [143]
Disinfectants		Ethylene oxide
Local anesthetics[b] [144]		Benzocaine, tetracaine, Xylocaine, mepivacaine
Others		Aminopyrine, sulfobromophthalein

[a]Numbers in brackets are reference citations.
[b]Precise mechanism not established.
ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

TABLE 194.2

CAUSES OF NON–IMMUNOGLOBULIN E-MEDIATED ANAPHYLAXIS[a]

Complement activation
Blood product transfusion in IgA-deficient patient [17]
Hemodialysis with cuprophane membrane [145]
Direct release of chemical mediators of anaphylaxis
Protamine [146][b]
Radiographic contrast media [147]
Dextran [148][b]
Hydroxyethyl starch [149]
Muscle relaxants [150]
Ketamine [151]
Local anesthetics [144][b]
Codeine and other opiate narcotics [150,152]
Highly charged antibiotics, including amphotericin B [143]
Generation of leukotrienes
Nonsteroidal anti-inflammatory drugs [132]
Indomethacin [133]
Acetylsalicylic acid (aspirin) [153]
Sulindac [134]
Zomepirac sodium [135]
Tolmetin sodium [136]
Other
Antineoplastic agents (e.g., platinum-based [154,155])
Sulfiting agents
Exercise [120]
Idiopathic recurrent anaphylaxis [124,126]

[a]Numbers in brackets are reference citations.
[b]Precise mechanism not established.

contraction of smooth muscle; (d) enhance prostaglandin synthesis; (e) chemotactically modulate eosinophil migration; and (f) regulate parasympathetic afferent nerve stimulation (a process blocked by atropine), which increases airway resistance and decreases lung compliance. Studies of histamine infusion in normal human volunteers suggest that vasodilatation is mediated by both H_1 and H_2 receptors, whereas bronchoconstriction and tachycardia are mediated by H_1 receptors alone [20].

In anaphylaxis, LTC_4, LTD_4, and LTE_4 (a) induce a prolonged constrictive effect, on bronchial smooth muscle, which affects the peripheral more than the central airways, (b) increase vascular permeability, and (c) act as chemotactic agents for other inflammatory cells [21,22]. In fact, leukotrienes are far more potent bronchoconstrictors than histamine.

Two additional modulators of anaphylaxis are bradykinin, which appears to be activated by mast cell kallikrein and PAF. Bradykinin stimulates a slow, sustained contraction of bronchial and vascular smooth muscles while increasing vascular permeability and secretion from mucous glands [15]. PAF contributes to the pulmonary and cardiovascular manifestations of anaphylaxis by inducing platelet aggregation with release of serotonin, adenosine triphosphate, and lysosomal enzymes from preformed granules [23,24]. In addition, PAF is a potent chemotactic factor for eosinophils and can directly increase vascular permeability [25].

Thus, the physiologic consequences of chemical–mediator release in anaphylaxis are (a) an increased vascular permeability; (b) an increased secretion from nasal and bronchiolar mucous glands; (c) smooth muscle contraction in the blood vessels, the bronchioles, the gastrointestinal tract, and the uterus; (d) migration–attraction of eosinophils and neutrophils; (e) bradykinin generation stimulated by kallikrein substances; and (f) induction of platelet aggregation and degranulation. These events coordinate to increase the vascular permeability that in turn permits the access of a variety of plasma proteins (antibodies, complement, kinins, and coagulation proteins) to tissue sites, which further contributes to the observed inflammation. Substances such as PAF and Hageman factor potentially contribute to local coagulation abnormalities, which may also be seen in anaphylactic reactions [20].

CLINICAL AND LABORATORY FEATURES

Mast cells are concentrated in the skin, in the mucous membranes of the respiratory and gastrointestinal tracts, and in the perivenular tissue, while basophils are located in the bloodstream, all of which are potential sites of exposure to offending antigens (e.g., food, drugs, insect venom, and diagnostic agents) [26]. These sites are also most commonly involved in the manifestations of anaphylaxis. Urticaria, angioedema, respiratory obstruction, and vascular collapse are the most important clinical features of anaphylaxis, and these signs and symptoms are due to the direct effects of mast cell and basophil-derived mediators on affected organ systems. Other clinical manifestations may include (a) a sense of fright or impending doom, (b) weakness or dizziness, (c) sweating, (d) sneezing, (e) rhinorrhea, (f) conjunctivitis, (g) generalized pruritus and swelling, (h) cough, (i) wheezing, stridor, or breathlessness, (j) choking, (k) dysphagia, (l) vomiting or diarrhea, (m) abdominal pain, (n) incontinence, (o) uterine cramps, and (p) loss of consciousness.

Profound hypotension and shock may develop as a result of significant arteriolar vasodilatation, increased vascular permeability, cardiac arrhythmias [27,28], or irreversible cardiac failure [29], even in the absence of respiratory or other symptoms [3,30]. Furthermore, transient or sustained hypotension may result in local tissue ischemia, stroke, myocardial infarction, or death [30,31]. Intravascular coagulation, evidenced by a fall in the levels of factors V, VIII, fibrinogen, kininogen, and complement components, has also been described [32].

Anaphylaxis-induced fatalities most often result from involvement of the respiratory tract [31,33,34]. Structures throughout the respiratory tract may be affected, but respiratory failure is generally the result of upper respiratory tract obstruction due to laryngeal edema or obstruction of small airways due to bronchoconstriction, mucosal edema, and hypersecretion of mucus [35,36]. Intra-alveolar hemorrhage and acute respiratory distress syndrome have been reported [36,37].

The physical examination of a patient with anaphylactic shock often reveals a rapid, weak, irregular, or unobtainable pulse; tachypnea, respiratory distress, cyanosis, hoarseness, stridor, or dysphagia secondary to laryngeal edema; diminished breath sounds, crackles, cough, wheezes, and hyperinflated lungs due to severe bronchoconstriction; urticaria; angioedema or conjunctival edema (Table 194.3) [38]. Any patient may manifest only a subset of these findings, sometimes only cardiovascular collapse or only stridor and breathlessness.

Laboratory findings in anaphylaxis are varied. Biochemical abnormalities in anaphylaxis include elevation of serum histamine and tryptase levels, depression of serum complement components, and decreased levels of high-molecular-weight kininogen. Although these biochemical abnormalities codify our understanding of the pathophysiology of anaphylaxis, they are rarely evaluated in the management of clinically established anaphylaxis. As discussed in the next section, serum tryptase may be helpful retrospectively when the diagnosis is uncertain [39].

Although there have been no systematic reviews of electrocardiographic findings, reports describe disturbances in rate,

TABLE 194.3

CLINICAL MANIFESTATIONS OF ANAPHYLACTIC REACTIONS

System	Reaction	Symptoms	Signs
Respiratory tract	Rhinitis	Nasal congestion and itching	Mucosal edema
	Laryngeal edema	Dyspnea	Laryngeal stridor, edema of vocal cords
	Bronchoconstriction	Cough, wheezing, and sensation of chest tightness	Crackles, respiratory distress, tachypnea, and wheezes
Cardiovascular	Hypotension	Syncope, feeling of faintness	Hypotension, tachycardia
	Arrhythmias	Palpitations	ECG changes: nonspecific ST segment and T-wave changes, nodal rhythm, and atrial fibrillation
Skin	Urticaria	Pruritus, hives	Urticarial lesions
	Angioedema	Nonpruritic swelling of extremity or perioral, or periorbital region	Nonpruritic, frequently asymmetric swelling of extremity, perioral, or periorbital region
Gastrointestinal tract	Smooth muscle contraction, Mucosal edema	Nausea, vomiting, abdominal pain, and diarrhea	Abdominal tenderness, distention
Eye	Conjunctivitis	Ocular itching, lacrimation	Conjunctival inflammation

ECG, electrocardiogram.
Summarized from references [38] and [1].

rhythm, repolarization, and ectopy [40–42], as well as myocardial infarction [28,43]. Chest radiography may reveal hyperinflation caused by severe bronchoconstriction.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ANAPHYLAXIS

Development of the characteristic clinical features of anaphylaxis shortly after exposure to an antigen or other inciting agent usually establishes the diagnosis of an anaphylactic reaction [2]. The setting is often suggestive as well: a patient who has just received an antibiotic injection or radiographic contrast media infusion or one who presents to the emergency room after a yellow jacket sting.

The clinical disorders that may be confused with anaphylaxis are sudden, acute bronchoconstriction in an asthmatic, vasovagal syncope, tension pneumothorax, mechanical airway obstruction, pulmonary edema, cardiac arrhythmias, myocardial infarction with cardiogenic shock, aspiration of a food bolus, pulmonary embolism, seizures, acute drug toxicity, hereditary angioedema, cold or idiopathic urticaria, septic shock, and toxic shock syndrome [15].

Initial laboratory testing often is not helpful. However, serum obtained during the acute episode can be assayed subsequently for tryptase and histamine. Total serum tryptase levels include both α- and β-tryptase. The former is increased in systemic mastocytosis and the latter can be elevated for up to 6 hours after suspected anaphylaxis onset [44]. However, the sensitivity of serum β-tryptase is suboptimal as levels can be normal after documented anaphylaxis, especially if caused by foods [45]. There may be a role for serial measurements in documenting the course of systemic mast cell and basophil degranulation [38]. Serum histamine is rarely assessed clinically because it must be obtained within the first hour after a reaction and requires special handling.

Retrospectively, measurement of antigen (allergen)-specific IgE antibodies by an ImmunoCAP (or similar assay, which have replaced radioallergosorbent tests [RAST]) may be helpful. Specific skin tests may also define allergic sensitivity. Skin testing must be done in a carefully controlled setting due to the risk of provoking another severe reaction. Cutaneous assessment for the presence of antigen-specific IgE may be negative for several days after a reaction, because mast cell and basophil degranulation at the time of the initial reaction may lead to a refractory period. This can be avoided by delaying testing for 4 to 6 weeks [46].

CLINICAL COURSE OF ANAPHYLACTIC REACTIONS

Clinical criteria that make the diagnosis of anaphylaxis "highly likely" have been codified [2]. The characteristic features of anaphylactic reactions are (a) the rapid onset of clinical manifestations that follow contact with or the administration of antigen and (b) the rapid progression of symptoms to a severe and potentially fatal outcome. Recognition of the early signs and symptoms of anaphylaxis and prompt treatment are imperative in preventing progression to irreversible shock and death [38].

The constellation of clinical symptoms as well as their severity and duration is variable but will depend to some extent on the mode of antigen exposure. Anaphylaxis may occur within seconds following parenteral introduction of antigen [32] and usually occurs within 30 minutes. In contrast, anaphylaxis that follows oral administration of an antigen may develop within minutes to several hours [47]. Generally, the more rapid the onset of symptoms, the more severe will be the reaction [1]. Mild systemic reactions often last for several hours, rarely more than 24 hours. Severe manifestations, such as laryngeal edema, bronchoconstriction, and hypotension, if not fatal, may persist or recur for several days. However, even severe manifestations may resolve within minutes of treatment. About 5% to 20% of patients will experience biphasic or protracted anaphylaxis, with signs and symptoms recurring up to 24 hours or persisting beyond 24 hours after initial presentation [38]. This highlights the need for close observation after initial response to treatment.

TREATMENT OF ANAPHYLAXIS

The key to successful treatment of anaphylaxis is prompt intervention to support cardiopulmonary function and prevent further exposure to the inciting stimulus when possible. The prompt administration of epinephrine is critical, and should be supplemented with aggressive use of vasopressors, fluid replacement, and medications as indicated to counteract the effects of released chemical mediators [38]. Injectable epinephrine, tourniquets, intravenous infusion materials and fluids, antihistamines, intubation equipment, a tracheostomy set, and individuals trained to use these materials should be available. Since symptoms of a systemic anaphylactic reaction may be followed by potentially fatal manifestations, patients must be serially examined and continuously monitored [38]. Many therapeutic and diagnostic agents frequently employed in intensive care settings (e.g., antibiotics, radiographic contrast) may induce anaphylactic reactions. Thus, the anticipation and the preparedness to deal with these potential reactions are very important.

Emergency Measures

The evaluation of individuals who are suspected of having anaphylaxis must be performed rapidly. The cause and mechanism of antigen exposure should be ascertained to assess how long the inciting antigen has been present and, when possible, to limit further absorption. A history of previous allergic reactions and former treatment may help to guide immediate therapy, obviating the need to try previously failed regimens in a life-threatening situation [48].

Supportive Cardiopulmonary Measures

Particular attention to the respiratory and cardiovascular systems is paramount and must include assessment for laryngeal edema and bronchoconstriction, as well as monitoring oxygenation, blood pressure, and cardiac rhythm [48].

Ensuring adequate ventilation and oxygenation is essential. Supplemental oxygen should be administered and pulse oximetry monitored. Intubation and assisted ventilation may be necessary in cases of severe bronchoconstriction, and ventilator management strategies such as those used for treatment of status asthmaticus may be necessary. These techniques are discussed in Chapters 48 and 58.

Although intubation is usually feasible, edema of the tongue, larynx, or vocal cords may obstruct the upper airway and preclude oropharyngeal or nasopharyngeal intubation. To ensure a patent airway in such instances, cricothyroidotomy or tracheotomy may be necessary (see Chapter 12) [49]. Cricothyroidotomy is preferred to tracheotomy when performed in an emergent situation, as the former is easier to perform and is usually safer [49]. Contraindications to cricothyroidotomy include a suspected neck fracture or a serious injury to the larynx or cricoid cartilage.

Close electrocardiographic monitoring is indicated because the sequelae of anaphylaxis and its therapy are both potentially arrhythmogenic [41]. Hypotension, acidosis, hypoxia, vasopressors, and bronchodilators are well-described predisposing factors for cardiac arrhythmias (see Chapter 42). Adequate intravenous access should be established as soon as possible, initially with two 18-gauge or larger peripheral catheters.

Pharmacologic Therapy

The mainstay of therapy is parenteral epinephrine (adrenaline), which acts on bronchial and cardiac β-receptors, causing bronchial dilatation and both chronotropic and inotropic cardiac stimulation. An equally important effect of epinephrine is stimulation of α-adrenergic receptors on blood vessels, which causes vasoconstriction. This is important in reversing anaphylaxis-induced hypotension and in delaying antigen absorption when infiltrated locally into an injection or sting site [48]. In addition, epinephrine increases the intracellular levels of cyclic adenosine monophosphate (AMP) and thereby inhibits the activation of tissue-based mast cells and circulating basophils [20,50,51]. Inhaled β_2-adrenergic agents, such as albuterol sulfate or salbutamol, complement the actions of epinephrine by reversing bronchoconstriction and reducing bronchial mucus secretion [52].

Antihistamines, particularly the H_1-receptor blocker diphenhydramine, are useful for treating cutaneous manifestations of anaphylaxis, but are slower in onset than epinephrine and not helpful for hemodynamic compromise. Thus, they are considered adjunctive therapy to epinephrine. Given their beneficial safety profile, they may be administered empirically unless there is a specific contraindication (e.g., known prior hypersensitivity). Glucocorticoids, although not immediately active in anaphylactic shock, are effective pharmacologic agents that are capable of increasing tissue response to β-adrenergic agonists as well as inhibiting basophil activation and phospholipase-mediated generation of LTC_4, LTD_4, and LTE_4 [53,54].

The guidelines for pharmacologic therapy of anaphylaxis are listed in Table 194.4.

Specific Therapy

Epinephrine. Epinephrine should be administered first to treat all initial manifestations of anaphylaxis [38,55]. When administered alone, it may reverse rhinitis, urticaria, bronchoconstriction, and hypotension. The failure to administer epinephrine or a delay in its administration may be fatal. There is compelling evidence, both from animal and human studies, that epinephrine is more rapidly absorbed when given intramuscularly (IM) rather than subcutaneously (SC) [56,57]. The IM route is definitely preferred for patients who are hypotensive (see below) or when adequate SC absorption is in doubt [58]. The dose is 0.2 to 0.5 mL of a 1:1,000 dilution (0.2 to 0.5 mg) and should be repeated in 5 to 15 minutes if improvement is equivocal, usually not more than three times [38,48]. Absorption of parenterally introduced antigens (e.g., stinging insect venom, vaccines) may be retarded by infiltrating the site with approximately half the dose of epinephrine. Tourniquet application proximal to the site of antigen exposure that is sufficient to occlude venous and lymphatic returns without interfering with arterial blood flow may also retard absorption of the antigen [1]. The tourniquet should be loosened for approximately 15 to 30 seconds every 10 to 15 minutes.

If shock develops, IM or SC epinephrine is unlikely to be absorbed. In this setting, epinephrine should be given intravenously: 1 mg (1 mL of a 1:1,000 solution or 10 mL of a 1:10,000 solution) diluted in 500 mL of D_5W and infused at a rate of 0.5 to 2.0 mL per minute (1 to 4 μg per minute) with continuous electrocardiographic monitoring. If intravenous access is not easily obtained, epinephrine should be given by endotracheal tube (10 mL of a 1:10,000 solution). If hypotension persists, continuous infusion of a pressor, such as norepinephrine, dopamine, or phenylephrine, is typically initiated (see Chapters 32, 148, and 157).

Volume resuscitation is also important, as described below. If no response to pressors and initial volume resuscitation occurs, the central venous pressure (CVP) may provide guidance regarding further fluid resuscitation. A CVP between 0 and 12 cm H_2O suggests that more intravenous fluids should be given, whereas a CVP more than 12 cm H_2O suggests that the hypotension may be based on myocardial failure. For

refractory hypotension, pulmonary artery catheterization (see Chapter 4) can help guide further fluid, inotropic, and vasopressor therapy, as outlined in Chapters 32,148, and 157.

Preexisting β-adrenergic blockade with noncardioselective or cardioselective agents is another potential cause of refractory anaphylactic shock [14,59]. In the presence of beta-blockade, anaphylaxis is characterized by bradycardia with or without atrioventricular nodal delay (in contrast to the usual tachycardia), profound and refractory hypotension, urticaria, and angioedema [59]. Whether beta-blockade truly increases the chance of developing anaphylaxis or just the severity is not known. Beta-blockade appears to increase anaphylactic mediator synthesis and release, as well as altering end-organ responsiveness. Although α-adrenergic agents may increase in vitro release of mast cell mediators in the presence of beta-blockade [60], the drug of first choice for treating anaphylaxis in the presence of beta-blockade remains epinephrine [59]. Dopamine, which has combined α, β, and dopaminergic activities, may be useful for shock refractory to epinephrine. The dose of β agonists will likely have to be more than usual to overcome the beta-blockade. Several case reports note the success with glucagon, often used in the treatment of beta-blocker overdose, in treating refractory shock. Glucagon appears to increase cardiac cyclic AMP independent of β-receptors and to increase heart rate despite beta-blockade [59,61].

Bronchodilators. Bronchoconstriction is treated with a nebulized short-acting β-agonist (typically albuterol 0.5 mL of 0.5% solution diluted in 3 mL of normal saline), often in addition to parenteral epinephrine, as described above. Nebulizer treatments should be repeated every 15 to 20 minutes until bronchoconstriction abates. In addition, a methylxanthine may be given: 250 to 500 mg of aminophylline may be infused over 20 minutes (see Chapter 48), although scientific data supporting this are limited. Methylxanthines are not recommended in hypotensive patients, as they may worsen hypotension and cause unpredictable cardiovascular toxicity [1]. Their exact mechanism of action is not well defined and they are not first-line agents in the treatment of bronchoconstriction.

Volume Resuscitation. Given the distributive nature of shock in anaphylaxis, aggressive volume resuscitation should accompany epinephrine (and other vasoactive medications) if hypotension develops. Prompt initiation of intravenous fluids is more important than whether the fluid is colloid or crystalloid. As noted earlier, refractory hypotension may warrant invasive hemodynamic monitoring to guide therapy.

Antihistamines. Parenteral administration of histamine receptor antagonists is preferred over oral administration. The H_1-receptor-blocker diphenhydramine (1 to 2 mg per kg up to 50 mg for an adult) can be given intravenously as a bolus [1]. The H_2-receptor-blockers cimetidine (300 mg for adult) or ranitidine (150 mg for adult) can be infused over 3 to 5 minutes [62]. Antihistamines are more effective in prevention than in treatment of full-blown anaphylaxis and should never be used as the primary therapy for anaphylactic shock. H_2-receptor-blocking antihistamines prevent the fall in diastolic blood pressure induced by experimental histamine infusion [54], and the H_2-blocker cimetidine has been reported to reverse refractory systemic anaphylaxis [62]. However, the evidence that H_2-receptor-blocking antihistamines are effective in the treatment of anaphylaxis is anecdotal.

Glucocorticoids. Although glucocorticoids are not of immediate clinical benefit, they help to reduce bronchoconstriction and laryngeal edema and provide blood pressure support when used in high doses and for prolonged attacks (see Table 194.4 for recommended doses). The generally recommended initial dose of aqueous hydrocortisone is 5 mg per kg to a maximum of 200 mg given intravenously, followed by 2.5 mg per kg to 200 mg given intravenously every 4 to 6 hours [1,4], for 24 to 48 hours.

Despite the theoretical basis for glucocorticoids preventing late recurrences of anaphylaxis, biphasic anaphylaxis has been reported to occur in 20% of anaphylactic reactions in spite of glucocorticoid therapy [63,64]. In this report, after an initial response to therapy, life-threatening symptoms recurred up to 8 hours later. Whether glucocorticoid therapy helped prevent recurrences after 8 hours, is not known. Because of the possibility of a late recurrence, patients should be monitored in the intensive care setting for 8 to 12 hours after resolution of symptoms. Roughly 30% of anaphylaxis cases may have protracted symptoms for 5 to 32 hours despite vigorous therapy including glucocorticoids [64]. One characteristic of patients with biphasic or protracted anaphylaxis is oral ingestion of the offending antigen. On this basis, it would be reasonable to include enteral activated charcoal and sorbitol in the therapy of such patients to reduce the absorption and duration of exposure to the antigen (see Chapter 117 on drug overdose).

TABLE 194.4

TREATMENT OF ANAPHYLAXIS IN ADULTS [2,38,156]

- Mandatory and immediate
  - General measures
    - Aqueous epinephrine (1:1,000), 0.2 to 0.5 mL IM; up to 3 doses at 1- to 5-min intervals
    - Tourniquet proximal to antigen injection or sting site
    - Aqueous epinephrine (1:1,000), 0.1 to 0.3 mL infiltrated into antigen injection or sting site (unless anatomic region with terminal circulation, e.g., fingertip)
  - For laryngeal obstruction or respiratory arrest
    - Establish airway: endotracheal intubation, cricothyroidotomy or tracheotomy
    - Supplemental oxygen
    - Mechanical ventilation
- After clinical appraisal
  - General measures
    - Diphenhydramine, 1.25 mg/kg to maximum of 50 mg, IV or IM
    - Aqueous hydrocortisone, 200 mg, or methylprednisolone, 50 mg, IV every 6 h for 24–48 h
    - Ranitidine, 150 mg, IV over 3–5 min
  - For hypotension
    - Aqueous epinephrine (1:1,000), 1 mL in 500 mL of saline at 0.5–2.0 mL/min, or 1–4 μg/min, preferably by a central venous line
    - Normal saline, lactated Ringer's, or colloid volume expansion
    - Glucagon, if patient is receiving beta-blocker therapy and hypotension is refractory, 1 mg/mL IV bolus or infusion of 1 mg/L of D_5W at a rate of 5–15 mL/min
  - For bronchoconstriction
    - Supplemental oxygen
    - Albuterol (0.5%), 0.5 mL in 2.5 mL of saline, by nebulizer
    - Aminophylline, only if patient *not* in shock and unresponsive to albuterol and epinephrine, 5 mg/kg to maximum or 500 mg IV over 20 min, then 0.3–0.8 mg/kg/h IV

D_5W, dextrose in 5% water; IM, intramuscular; IV, intravenous.

PREVENTION OF ANAPHYLACTIC REACTIONS

In view of the potential morbidity and mortality from anaphylactic reactions, prevention is of primary importance. Prevention includes obtaining a careful history to identify possible precipitants of anaphylaxis. Both physicians and patients should be aware of potential cross-reacting agents. For example, individuals with anaphylaxis secondary to aspirin are frequently sensitive to nonsteroidal anti-inflammatory drugs, such as ibuprofen, naproxen, ketorolac, and sulindac. Other preservatives, such as metabisulfite, ethylenediamine, and methylparaben, have been associated with anaphylactic reactions. It is therefore helpful to review the inactive ingredients contained in medications temporally associated with anaphylaxis [65].

Prevention of reactions to specific agents (e.g., antibiotics) is discussed below. In general, patients with a history of anaphylaxis should wear a Medic-Alert bracelet or necklace, which detail offending precipitants and potential cross-reacting agents. In addition, patients should be provided with and instructed in the use of anaphylaxis kits (e.g., EpiPen, Dey, Napa, CA) for prompt treatment in future reactions. Finally, consultation with an allergist can clarify the offending trigger (if unknown) and guide appropriate further evaluation and treatment plans. These three actions are the most relevant elements of post-anaphylaxis care from the intensive care perspective.

MANAGEMENT OF ANAPHYLAXIS TO SPECIFIC AGENTS AND PRECIPITANTS

Beta-Lactam Antibiotic Anaphylaxis

One of the most common causes of anaphylaxis in the United States is penicillin. Systemic reactions complicate approximately 1% to 2% of penicillin courses. Approximately 10% of the population will have positive skin tests to penicillin. Thus, a substantial portion of the population is at risk for developing anaphylactic reactions to the drug. About 10% of these reactions are life-threatening and 2% to 10% are fatal [16]. Seventy-five percent of the patients who die of penicillin anaphylaxis have experienced previous allergic reactions to the drug. As with other medications, the risk of a severe reaction is greater with parenteral administration than with oral administration [16]. On the other hand, about 80% of individuals who report penicillin allergy are found to be nonallergic on subsequent evaluation [66].

Skin testing for penicillin hypersensitivity with the major determinant benzylpenicilloyl-poly-l-lysine (BPO, PRE-PEN®, and ALK-Abello) and minor determinants benzylpenicillin (Pen-G), benzylpenicilloate, and benzylpenilloate is effective at detecting IgE-mediated sensitivity and thereby identifying individuals at risk for developing acute allergic reactions to penicillin [16]. The negative predictive value of skin testing when both major and minor determinants of penicillin are used is excellent for immediate hypersensitivity reactions to penicillin [66,67]. This testing does not evaluate other types of sensitivity, such as serum sickness reactions, morbilliform rashes, hemolytic anemia, and interstitial nephritis. In addition, it does not evaluate patients who may have specific allergy to a beta-lactam side chain of a penicillin derivative, for example, cephalosporins or carbapenems [68]. Cross-reactivity between beta-lactams and monobactams, for example, aztreonam, is rare. For critically ill patients, who need a beta-lactam drug and who have a history of beta-lactam antibiotic allergy, the best strategy is to use an alternate, non cross-reacting antibiotic or to proceed with a rapid desensitization protocol [69] (Table 194.5). A retrospective review of antibiotic desensitization for IgE-mediated allergy found that it was successful in 75% of patients [70].

TABLE 194.5

DESENSITIZATION SCHEDULE FOR BETA-LACTAM ANTIBIOTICS

Dose no.	Concentration of stock solution (mg/mL)[a]	Concentration of infused solution (mg/mL)[b]
1	0.0005	0.00001
2	0.005	0.0001
3	0.05	0.001
4	0.5	0.01
5	5	0.1
6	50	1
7	500	10

[a] Stock solution is prepared by solubilizing the antibiotic with nonbacteriostatic saline to a final concentration of 500 mg/mL. Dilutions of 1 mL of each preceding antibiotic dilution to 9 mL of diluent.
[b] One milliliter of stock solution is further diluted into 50 mL of saline and infused during 20 minutes.
From Borish L, Tamir R, Rosenwasser LJ: Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol* 80:314–319, 1987, with permission.

The incidence of anaphylactic reactions to cephalosporins is infrequent, but increasing [16,71]. Patients with a history of penicillin allergy have been reported to have allergic reactions to cephalosporins at a rate of 5.4% to 16.5%, compared with patients with a negative history, whose reaction rate was 1% to 2% [72,73]. The rate of cross-reactivity is lower with second- and third-generation than with first-generation cephalosporins. However, not all of these reactions reflect true cross-reactivity, as only 15% to 40% of patients with a positive history react to penicillin on subsequent testing [72,74]. In a study of 30 patients with immediate-type hypersensitivity reactions to second- and third-generation cephalosporins, 25 of 36 reactions were anaphylactic shock [75]. Only 13% of individuals had either a positive skin test or *in vitro* evidence of antigen-specific IgE to penicillin determinants, while all but three reactions were correlated with a positive skin test to culprit cephalosporins. Unfortunately, skin testing with cephalosporin derivatives is not reliable; severe allergic reactions have occurred in patients with negative cephalosporin skin tests and cephalosporin antigenic determinants for skin testing have not been standardized. On the other hand, patients with negative penicillin skin tests have no greater risk of allergic reaction to cephalosporins than the general population [73]. Several protocols for desensitization to cephalosporins have been outlined in a review [76]. Cross-reactivity between cephalosporins appears related to the degree of similarity of the R1 side chains, and 90% of patients allergic to second- and third-generation cephalosporins do not react to penicillin derivatives [71].

As noted earlier, monobactams (e.g., aztreonam) do not show cross-reactivity with penicillin, but do show some cross-reactivity with the cephalosporins (i.e., ceftazidime) [71]. Carbapenems (e.g., imipenem, meropenem), in comparison, have historically shown significant *in vivo* cross-reactivity with penicillin, and desensitization in penicillin-allergic patients was recommended when there was no reasonable alternative [77]. More recent reports in PCN skin test–positive patients have suggested that carbapenems can be given safely to young

[78,79] and adult [80] patients, who have negative skin tests to the proposed carbapenem. In urgent settings and/or where skin testing and graded challenge are not feasible, a desensitization protocol should be employed with the same precautions as if giving the patient penicillin [73].

Food Anaphylaxis

Food allergy occurs in approximately 6% of children and 3.7% of adults [47]; however, fatal anaphylactic reactions are much less common. Due to variable patterns of absorption, biphasic and/or prolonged anaphylaxis occurs in about 20% of cases. However, the delayed phase is rarely associated with a mild acute phase, where hypotension and bronchoconstriction are readily apparent [81]. A review of fatal and severe nonfatal anaphylactic reactions to foods revealed several important features of the fatal anaphylactic reactions: all occurred in patients with asthma, all were in a public setting rather than in the home, and all were associated with delayed administration of epinephrine [82]. The foods that caused these severe reactions were peanuts, cashews, milk, filberts, walnuts, and eggs. In another review of the causes of anaphylaxis, the five most common foods were pine nuts, peanuts, soy, shellfish, and other nuts [83]. A survey of food-related anaphylactic fatalities reported to an association registry confirmed the association between asthma and severe anaphylaxis; 90% of fatalities in this group were due to peanuts and tree nuts [34]. A methodical approach to the diagnosis and treatment of food hypersensitivity has been outlined by Sicherer and Sampson [47].

Processed foods may contain significant amounts of milk products, despite a lack of mention of this on the label ingredient lists [84]. This is important to remember in patients with milk allergy who appear to experience a cryptogenic anaphylactic episode. Standards for food labeling instituted in 2006 by the U.S. Food and Drug Administration have assisted patients with food allergy and their providers by requiring identification of possible trace allergen contaminants in processed foods. Other food additives, such as preservatives, have been implicated as causes of anaphylaxis [85].

Anesthetic Anaphylaxis

Immediate hypersensitivity reactions to local anesthetics are rare, despite them being one of the most commonly used groups of drugs in medicine [86,87]. Cell-mediated reactions that manifest as contact dermatitis are more common. Local anesthetics are divided into two classes: group I (para-aminobenzoic acid ester) consists of benzocaine, tetracaine, and procaine; group II (non–ester-containing) consists of Xylocaine, mepivacaine, dibucaine, and cyclomethycaine. Cross-reactivity between the two groups is very rare and cross-reactivity between the amides is also rare [88,89]. Skin testing, using a progressive challenge protocol, can help determine whether sensitivity exists and which drugs are likely to be safe in the future [87,89].

General anesthetics, such as neuromuscular blocking agents and thiobarbiturates, also cause anaphylaxis [90]. A skin test protocol has been described for evaluating patients with possible allergy to general anesthetics [91]. Other etiologies of perioperative anaphylaxis include allergy to antibiotics, latex, glutaraldehyde, and opioids.

Since neuromuscular blocking agents are used in intensive care units, anaphylaxis to these agents should be considered in the differential diagnosis of unexplained hypotension in the intensive care unit.

Radiocontrast Media Anaphylaxis

Radiocontrast dye studies are frequently necessary in critically ill patients, so it is important to know when a reaction is likely to occur and how to prevent it. Unfortunately, the likelihood of an anaphylactic reaction to radiocontrast dye cannot be predicted by pretesting with oral, conjunctival, or intradermal skin tests [92]. Although the overall adverse reaction rate ranges from 1% to 12% [93], patients with a history of a previous anaphylactic reaction to radiocontrast dye have a repeat reaction rate of 35% to 60% [94]. Patients with a general history of allergies, whether to inhalant allergens, foods, or medications, also have an increased reaction rate of serious reactions compared with nonallergic individuals [95]. The majority of contrast dye reactions are non-IgE mediated, although evidence is accumulating to suggest that an IgE-mediated mechanism may be contributory in some cases [96,97]. Although exceedingly rare, there have been several confirmed reports of anaphylactic reactions to iodinated oral contrast: Gastrografin (sodium and meglumine diatrizoate), Hypaque (sodium diatrizoate), barium sulfate, and gadolinium [98–102].

Nonionic, low-osmolal radiocontrast agents have largely replaced high ionic contrast media due to a decreased incidence of overall adverse reactions [103,104], although not all studies have found a reduction in life-threatening reactions or death [105,106]. Currently, for patients who have had a prior anaphylactic reaction to contrast media and who require a contrast study, the use of nonionic, low-osmolal contrast is recommended in addition to pretreatment with glucocorticoids, diphenhydramine with or without ephedrine [107], as outlined below. Iso-osmolal and noniodinated contrast are also being explored as alternatives to low-osmolal agents [107,108].

Pretreatment protocols have been developed for patients with a history of a prior anaphylactic reaction who require additional intravascular dye studies [92,94,109]. In one study of 192 procedures in patients with previous anaphylactic reactions to contrast media, pretreatment with prednisone, 50 mg orally at 13 hours, 7 hours, and 1 hour before the procedure, diphenhydramine, 50 mg orally or intramuscularly at 1 hour before the procedure, and ephedrine, 25 mg orally at 1 hour before the procedure resulted in a reaction rate of 3.1% [94]. A multicenter study of nonselected patients receiving intravenous contrast media reported a reaction rate of 5.4% in 2,513 patients given oral methylprednisolone, 32 mg at 12 hours and again at 2 hours before the procedure [109]. In this same study, a single dose of methylprednisolone, 32 mg 2 hours before the procedure, was no better than placebo, with a reaction rate of 9.4% in 1,759 patients. This finding raises the question of how to manage patients with a prior history of anaphylaxis requiring an urgent radiocontrast study. In a small study, nine such patients were treated with hydrocortisone, 200 mg intravenously immediately and every 4 hours until the procedure was completed, and diphenhydramine, 50 mg intravenously 1 hour before the procedure [110]. Roughly half of the patients received one dose of hydrocortisone, and the other half received two doses. No reactions occurred in these patients. Given that this study evaluated only nine patients, it remains unknown whether additional therapy with ephedrine or an H_2-receptor blocking agent, or both, would provide better protection.

Latex-Induced Anaphylaxis

Latex allergy, caused by sensitivity to *Hevea brasiliensis* proteins, can take several forms: contact dermatitis, asthma, urticaria, and anaphylaxis. Perioperative anaphylaxis caused by latex exposure has been described in several children with *spina bifida* and in patients with a history of multiple surgical

procedures [111]. In addition, latex allergy has become an occupational hazard in the health profession since the institution of universal precautions [112]. Sensitivity seems to be increased in atopic individuals with frequent exposure to latex. Unexplained perioperative or nosocomial urticaria, bronchoconstriction, or hypotension should raise concern for latex anaphylaxis. Mucosal and parenteral exposures have the highest risk of anaphylaxis.

Patients with latex allergy often have cross sensitivity with certain fruits and vegetables, including banana, kiwi, avocado, chestnut, papaya, potato, and tomato. Latex is found in a wide spectrum of health care products, including elastic thread, rubber bands, condom catheters, Foley catheters, surgical/examination gloves, enema bags, tubing on blood pressure cuffs, rubber stoppers on medication vials and intravenous line tubing, as well as some surgical drapes, drains, and gowns [113–116].

Establishing a diagnosis of latex allergy in a patient who is at high risk based on prior exposures or who may have had latex-induced anaphylaxis is important to guide future prevention efforts. However, skin test extracts are not yet commercially available in the United States and noncommercial latex extracts have been associated with systemic reactions. In addition, the specificity and sensitivity of noncommercial extracts may vary. A preferred alternative is serological testing by Phadia ImmunoCAP or the Siemens Immulite autoanalyzer; these tests have about 80% sensitivity [114,115].

The most important steps in prevention of future anaphylactic reactions to latex are careful patient education and in-hospital latex avoidance through the use of alert bracelets and latex-free kits [90]. Verbal and written information should be provided regarding potential sources of latex exposure and sources of latex-free gloves for patients to take to dentist and doctor visits. In addition, patients should understand the importance of alerting health care professionals who may care for them in the future and the need to carry an EpiPen kit in case of inadvertent exposure.

Stinging Insect Venom Anaphylaxis

Venom extracts for yellow jacket, white-faced hornet, yellow-faced hornet, wasp, honeybee, and fire ant are available for skin testing to confirm specific IgE mediation and for desensitization. Results with venom desensitization suggest more than 95% protection against anaphylaxis on subsequent stings [85]. The duration of desensitization therapy necessary for long-term protection is probably 5 years [117,118]. The geographic distribution of fire ants is expanding, making systemic allergic reactions to these insects a growing concern [119].

Exercise-Induced Anaphylaxis

Exercise-induced anaphylaxis syndrome is distinct from cold and cholinergic urticaria and exercise-induced asthma and usually occurs in individuals who engage in vigorous exercise [120,121]. A subgroup of these patients is allergic to a specific food, such as shrimp or celery, which acts as a cofactor; manifestations of anaphylaxis only occur if ingestion of the specific food is accompanied by exercise. Other potential cofactors include nonsteroidal anti-inflammatory drugs (NSAIDs), alcoholic beverages, and exposure to high pollen counts [122,123]. Typically, these patients can either ingest the food/NSAID or perform the exercise without adverse effect.

Anaphylaxis can be prevented by delaying exercise by at least 2 and preferably 4 hours after eating (48 hours after ingesting a food cofactor) and stopping exercise at the onset of pruritus. When NSAIDs are a cofactor, they should not be taken for at least 24 hours prior to exercise. Exercising with someone who is capable of administering epinephrine is also recommended. Antihistamines are occasionally of benefit in prevention.

Idiopathic Anaphylaxis

A group of patients has been described who experience recurrent anaphylaxis without an identifiable precipitant, the so-called *idiopathic anaphylaxis* [124]. In these patients, a careful review of all foods, preservatives, and drugs ingested prior to the episodes, as well as physical factors such as exercise, fails to reveal a cause for recurrent life-threatening anaphylaxis. These patients should be evaluated for possible systemic mastocytosis [125]. Maintenance therapy with antihistamines,

TABLE 194.6

MANAGEMENT OF ANAPHYLAXIS—QUALITY OF THE EVIDENCE

History of exposures and timing is the most important information to determine whether a set of symptoms was due to anaphylaxis and what tripper precipitated the event. (C)

The appropriate dose of epinephrine should be administered promptly at the onset of anaphylaxis. (A/D)

Intravenous infusion of crystalloid or colloid is essential for patients who are unstable or refractory to initial therapy with epinephrine. (B)

Specific situations

The extent of allergic cross-reactivity between penicillin and cephalosporins is low. (C)

Aztreonam cross-reacts with ceftazidime by shared R-group side chain. (B)

The three groups at increased risk for latex anaphylaxis are health care workers, children with *spina bifida* and genitourinary problems, and workers with occupational exposure to latex. (B)

Precautions for latex-allergic patients undergoing anesthesia include avoiding latex gloves, latex blood pressure cuffs, latex tourniquets, latex intravenous tubing ports, and rubber stoppers on vials. (B)

The greatest number of anaphylactic reactions in children has involved peanuts, tree nuts, fish, shellfish, milk, and eggs. (C)

Anaphylactic reactions to foods almost always occur immediately, but may recur hours later. (A)

Strength of recommendation

A. Directly based on meta-analysis of randomized controlled trials or from at least one randomized controlled trial or systematic review of randomized controlled trials/body of evidence.
B. Directly based on at least one controlled trial without randomization or at least one other type of quasi-experimental study or extrapolated recommendation from A.
C. Directly based on at least one other type of quasi-experimental or descriptive/comparative study or extrapolated recommendation from A or B.
D. Directly based on evidence from expert committee report or opinions or clinical experience of respected authorities or both.

Summarized from reference [38] and others.

oral glucocorticoids, and sympathomimetics has been shown to reduce the frequency and severity of episodes of this disorder [126,127].

Angiotensin-Converting Enzyme Inhibitor Angioedema

Severe, potentially life-threatening facial and oropharyngeal angioedema may occur in individuals with hypersensitivity to angiotensin-converting enzyme (ACE) inhibitors [128–130]. Onset of angioedema usually starts within the first several hours or up to a week after beginning therapy, but angioedema can develop after months to years of asymptomatic usage [128]. Subsequent episodes may occur after days to weeks of continued usage. A late onset of symptoms, 12 to 24 hours after the last dose, has been reported with the long-acting ACE inhibitors lisinopril and enalapril [130]. As with ACE-induced cough, cross-reactivity is the rule among different ACE inhibitors. The mechanism is unknown but is suspected to be related to an alteration in bradykinin metabolism or, possibly, an interaction with components of the complement cascade (e.g., complement 1-esterase inhibitor) [131].

Aspirin and NSAIDs

Acetylsalicylic acid (aspirin) and nonsteroidal anti-inflammatory agents cause urticaria, flares of urticaria in patients with chronic idiopathic urticaria, anaphylaxis, and aspirin-exacerbated respiratory disease (AERD) [132–136]. Most patients have either the urticaria/anaphylaxis pattern or the respiratory disease pattern, but a few patients have both. Some patients with the urticaria/anaphylaxis pattern appear to have sensitivity to a particular NSAID, but most have cross-sensitivity that is related to an abnormality of prostaglandin/leukotriene metabolism [137]. Desensitization protocols for patients with coronary artery disease, who need the antiplatelet effects of aspirin, have been published [138,139].

Miscellaneous Causes of Anaphylaxis

Insulin therapy has been associated with an increased risk of anaphylaxis, particularly when a patient on insulin therapy has a history of local wheal-and-flare reactions at the site of insulin injections and interrupts insulin therapy for more than 48 hours and then resumes it [16,140]. Anaphylaxis has also been described with recombinant DNA insulin [141] and to protamine in neutral protamine Hagedorn (NPH) insulin [142].

The injection of heterologous serum carries a significant risk of anaphylaxis. Human serum (homologous) should be used whenever available. If heterologous serum must be used (antitoxin for snake bites, passive rabies immunization in developing countries, and antilymphocytic serum for organ transplantation), patients are usually evaluated for cutaneous sensitivity by first performing a scratch test with antitoxin or normal horse serum. If there is no reaction, 0.02 mL of a 1:10 serum dilution can be injected intradermally. As with all skin testing, the physician must be prepared to treat any systemic reactions that arise [1].

Patients with mastocytosis appear to be at greater risk for developing anaphylaxis from Hymenoptera stings (even in the absence of IgE mediation) and from mast cell degranulating agents (see Table 194.2). These patients should carry an epinephrine kit during Hymenoptera season. Administration of diagnostic and therapeutic agents that might cause mast cell activation should be avoided in these patients.

The quality of evidence and recommendations for diagnosis and management of anaphylaxis are summarized in Table 194.6.

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CHAPTER 195 ■ DERMATOLOGY IN THE INTENSIVE CARE UNIT

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INTRODUCTION

Patients in the intensive care unit (ICU) often present with cutaneous findings. Their reason for admission to the ICU may be primarily dermatologic, as in the case of toxic epidermal necrolysis (TEN) or pemphigus vulgaris, two diseases in which large areas of the epidermis are shed. Or they may have skin findings that provide diagnostic clues to their internal disease, as when a patient with systemic lupus erythematosus presents with a classic malar rash. Patients with life threatening infections, such as Rocky Mountain spotted fever and Meningococcemia, may present with characteristic skin lesions that suggest the correct diagnosis and allow prompt institution of lifesaving treatment.

Skin conditions in ICU patients are often iatrogenic, being caused by drugs (e.g., TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP)), procedures (e.g., cholesterol emboli), dressings (e.g., contact dermatitis), or inattentive care (e.g., pressure ulcers). At other times, patients may have skin conditions which, although relatively minor, may complicate their ICU stay, put other patients and health care workers at risk (e.g., scabies), or make patients uncomfortable (e.g., miliaria, Grover's disease).

In this chapter, we give an overview of serious illnesses with prominent cutaneous findings, including drug reactions, exfoliative erythrodermas, infections, blistering disorders, vascular disorders, connective tissue disorders, and graft-versus-host disease (GVHD). In addition, we provide a brief description of more common but less serious dermatoses that may coexist in ICU patients, with suggestions for their management. We emphasize the importance of lesion morphology, that is, the shape, color, size, arrangement, and distribution of skin lesion in making a correct diagnosis. Table 195.1 provides a list of skin diseases arranged by morphology to assist in formulating a differential diagnosis.

Dermatologic consultation is often helpful for diagnosis and management of skin diseases in ICU patients. The dermatologic consultant may be able to help sort out multiple potential differential diagnoses by inspection of morphology, skin biopsy, or use of other diagnostic tests (skin scrapings for scabies, potassium hydroxide preparations for fungus, viral and bacterial cultures, direct fluorescent antibody tests for viral infections, etc.) Since morphology evolves with the natural course of disease and with attempted therapeutic measures, it is helpful to request consultation early in the course of cutaneous disease.

DRUG ERUPTIONS

Cutaneous drug reactions are frequently encountered in ICU patients. Certain drug reactions such as toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), DRESS, and acute generalized exanthematous pustulosis (AGEP) may be the primary cause for admission to the ICU. These reactions will be discussed in depth following a brief overview of more commonly occurring drug reactions. The exanthematous or morbilliform drug eruption is the most common (Fig. 195.1). It typically appears 7 to 14 days after introduction of the offending agent. Clinically it appears as symmetric macules that may become slightly papular on the trunk and upper extremities, and may become confluent with time. Low-grade fever and pruritus are sometimes present. The differential diagnosis includes viral exanthem, Kawasaki's disease, GVHD, and the more serious drug reactions discussed below (TEN, SJS, DRESS, and AGEP). Facial edema, mucosal lesions, blisters or sloughing of the skin, and laboratory abnormalities such as neutrophilia, eosinophilia, and elevated liver function tests may indicate the presence of a more serious drug reaction. Withdrawal of the causative drug is the most important treatment, although topical corticosteroids and oral antihistamines may be used for symptomatic relief. Exanthematous drug eruptions resolve without sequelae 1 to 2 weeks after the offending drug has been discontinued.

Toxic Epidermal Necrolysis/ Stevens–Johnson Syndrome

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are entities on a spectrum of severe cutaneous reactions that are most commonly caused by medications. They exhibit severe blistering and sloughing of the skin (Fig. 195.2) with mucosal involvement (Fig. 195.3), and may have high morbidity and mortality. The distinction between TEN and SJS is based on the percentage of skin involved with SJS being $< 10\%$, TEN being $> 30\%$, and SJS/TEN overlap being 10% to 30% of the body surface area affected. The cumulative annual incidence of these entities has been estimated at 1.89 per million people. SJS is more common in children, whereas TEN is more common in adults. TEN is more common in women, and the incidence increases with age and immunosuppression [1]. HIV infection increases the risk of SJS/TEN with the incidence of TEN in HIV patients receiving trimethoprim-sulfamethoxazole, 8.4 per 100,000 exposures as opposed to 2.6 per 100,000 exposures in non-HIV infected individuals [2]. There appears to be a genetic component to SJS/TEN, as multiple studies have demonstrated HLA alleles related to hypersensitivity to specific medications, however, at this time human leukocyte antigen (HLA) testing is not clinically useful due to its expense [2].

Ninety five percent of patients with TEN have a history of drug exposure and there is a clear relationship to a drug in 80% of cases. Only half of SJS cases are related to medications with the remainder being attributed to infections, including mycoplasma, which may present as mucositis without typical skin manifestations. The most common causative medications along with relative risks listed in parentheses include: trimethoprim-sulfamethoxazole (172), carbamazepine

TABLE 195.1

DIFFERENTIAL DIAGNOSIS OF SKIN ERUPTIONS BY MORPHOLOGY

Fever and rash
- Infectious disease (bacterial, fungal, viral)
- Rheumatologic disease (SLE, rheumatoid arthritis, juvenile rheumatoid arthritis, Still's disease, mixed connective tissue disease)
- Pustular psoriasis
- Drug eruption
- Leukemia/lymphoma
- Lofgren's syndrome (acute sarcoidosis with erythema nodosum, hilar adenopathy, fever, and arthritis)
- Sweet's syndrome
- Polyarteritis nodosa

Morbilliform (maculopapular)
- Drug eruption
- Viral exanthem
- Graft-versus-host disease
- Rickettsial infections

Generalized erythema
- Staphylococcal scalded skin syndrome
- Exfoliative erythroderma

Localized erythematous papules and plaques
- Psoriasis
- Seborrheic dermatitis
- Contact dermatitis
- Pityriasis rosea
- Tinea
- Scabies
- Dermatomyositis
- Lupus erythematosus
- Secondary syphilis
- Urticaria
- Still's disease
- Disseminated candidiasis
- Erythema nodosum
- Grover's disease

Annular (ring-shaped) erythematous lesions
- Tinea
- Erythema multiforme
- Urticaria
- Granuloma annulare
- Sarcoid
- Subacute cutaneous lupus
- Sweet's syndrome
- Erythema chronicum migrans (Lyme disease)
- Leprosy

Pustules
- Pustular psoriasis
- Steroid acne
- Folliculitis
- Acute generalized exanthematous pustulosis (AGEP)

Vesicles/Bullae
- Herpes simplex
- Varicella zoster
- Miliaria
- Bullous infections (impetigo, tinea, cellulitis)
- Erythema multiforme/Stevens–Johnson syndrome/TEN
- Pemphigus
- Paraneoplastic pemphigus
- Bullous pemphigoid
- Linear IgA dermatosis
- Epidermolysis bullosa acquisita
- Porphyria cutanea tarda
- Dermatitis herpetiformis

Purpura
- Vasculitis
- Purpura fulminans
- Calciphylaxis
- Heparin or Coumadin necrosis
- Cryoglobulinemia
- Cholesterol emboli
- Myeloproliferative disease
- Antiphospholipid syndrome

Ulcers
- Vasculopathy
- Infectious
- Neoplastic
- Bullous disorders
- Panniculitis
- Neuropathy
- Bites
- Aphthae
- Trauma

(90), NSAIDS (72), corticosteroids (54), phenytoin (53), allopurinol (52), phenobarbital (45), valproic acid (25), cephalosporins (14), quinolones (10), and aminopenicillins (6.7), with more recent reports implicating lamotrigine, rituximab, imatinib, lenalidomide [3]. The time from drug ingestion to clinical symptoms is generally 1 to 3 weeks, except for the aromatic anticonvulsants that can take up to 2 months to cause disease [4].

The cutaneous eruption may be heralded by a 1 to 3 day prodrome of fever and flu-like symptoms. The initial cutaneous finding is irregularly shaped erythematous to purpuric macules with irregular size and shape distributed on the face and trunk. This may evolve into flaccid blisters that may be easily enlarged with lateral pressure. The skin can become gray, which usually heralds full thickness epidermal sloughing. Mucosal involvement is present in 90% of patients with SJS and TEN, with the most common affected areas being the conjunctiva, oral cavity, and genitalia. Symptoms include severe skin pain and difficulty swallowing and urinating. Respiratory epithelium may also be involved with resultant dyspnea, pulmonary edema, and hypoxia.

The differential diagnosis includes staphylococcal scalded skin syndrome (SSSS), acute generalized exanthematous pustulosis (AGEP), severe acute GVHD, drug-induce linear IgA bullous dermatosis, and paraneoplastic pemphigus. The appropriate clinical setting and skin biopsy easily differentiate SJS/TEN from these entities. Two skin biopsies are recommended, one for frozen section and the other for routine H&E. Early lesions demonstrate necrotic keratinocytes, while advanced lesions reveal full-thickness epidermal necrosis, and a recent study indicates that the density of the dermal mononuclear cell infiltrate correlates with the severity of disease and mortality rate [5].

Prompt diagnosis and rapid cessation of the causative medication along with supportive therapy is the cornerstone of

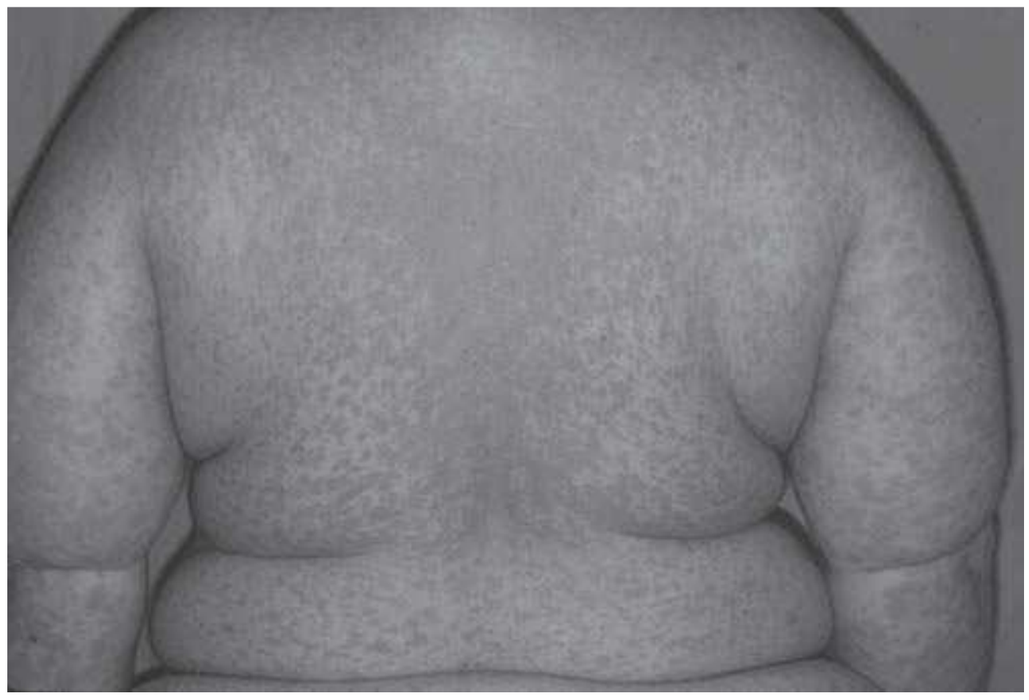

FIGURE 195.1. Morbilliform (maculopapular) drug eruption. Note the pink blanchable papules and plaques with areas of confluence over the trunk and extremities.

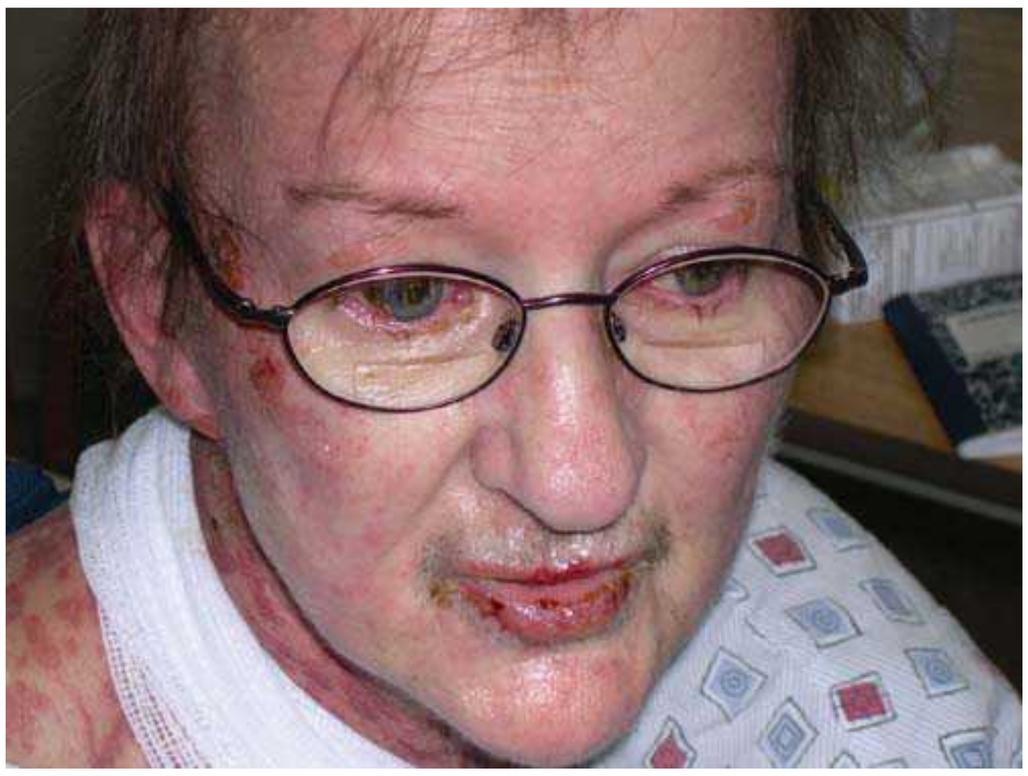

FIGURE 195.3. Stevens–Johnson syndrome. Bullae over the left top eyelid and erythematous and edematous plaques on the neck and shoulders. Note the erosions over the lips.

therapy. Careful monitoring of fluid volume, electrolytes, renal function, nutritional status, and evaluation for signs of sepsis should be performed. For extensive body surface involvement, care should be provided in an ICU with staff accustomed to caring for patients with fragile and denuded skin, usually a burn unit. Uninvolved skin should not be manipulated, while involved skin should be covered with Vaseline impregnated gauze and a topical antibiotic ointment. Debridement of necrotic skin may be followed by placement of artificial membranes or biologic dressings such as xenografts or allografts. Daily bacterial cultures should be performed of involved skin and mucosa as well as blood, urine, and any intravenous catheters, as sepsis is the most common cause of mortality in patients with SJS/TEN. Systemic antibiotics should not be started unless signs of sepsis are present because of the risk of selecting for antibiotic resistant organisms, and prophylactic use of antibiotics has not been shown to improve outcome [2]. Patients should be followed by an ophthalmologist to avoid conjunctival scarring. Currently, there is no gold standard systemic therapy for TEN/SJS. Intravenous immunoglobulin (IVIG) has been used, based on its ability to bind Fas receptors, thought to be a major mediator of apoptosis in TEN/SJS. Unfortunately, there are no randomized double-blind trials to support its use, and while some studies have shown mortality benefit with doses more than 1 g per kg per day, others have shown no benefit or even increased mortality associated with its use [6]. Systemic corticosteroid pulse therapy early in the disease course has been shown to have benefit in preventing ocular complications, and topical high potency corticosteroids appear to prevent corneal epithelial stem cell loss and scarring [7]. There is some emerging evidence that high dose (1.5 mg/kg/day) pulse corticosteroids decreased TEN-associated mortality [2]. Other systemic treatments have been tried, but none are recommended at this time [8].

The mortality rate for SJS and TEN is 5% and 30%, respectively, and is directly related to the percentage of skin involved. Risk of mortality can be predicted using the SCORTEN algorithm. One point each is assigned for the presence of the following seven criteria: age > 40 years, presence of malignancy, heart rate > 120, initial epidermal detachment > 10%, serum urea nitrogen > 10 mmol per L, serum glucose > 14 mmol per L, and serum bicarbonate < 20 mmol per L. The points are added and the predicted mortality based upon this total is 0 to 1 (3.2%), 2 (12.1%), 3 (35.8%), 4 (58.3%), and 5 or more (90%) [9]. Healing of sloughed epidermis usually takes 3 weeks and survivors may experience ocular scarring and visual loss. If the causative medication is reintroduced, the disease may recur in less than 48 hours. Notably, a patient who experiences TEN to one class of medication is not predisposed to TEN in response to other medication classes; however, cross-reactivity may be seen between related drug classes such as penicillins and cephalosporins.

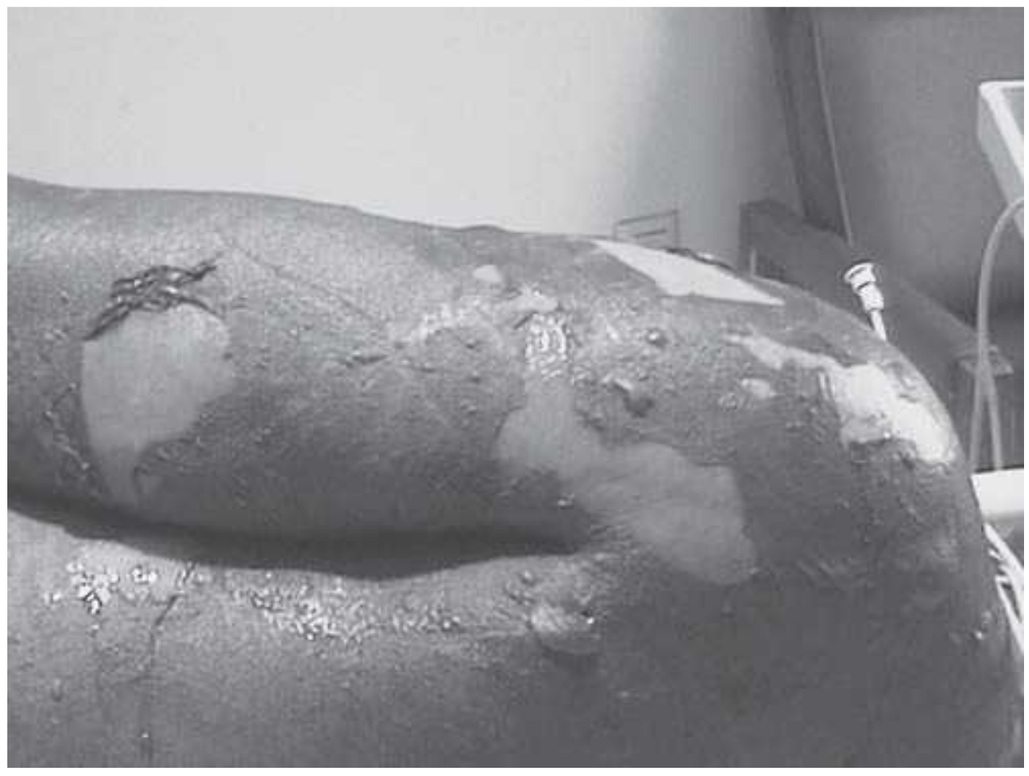

FIGURE 195.2. Toxic epidermal necrolysis. Bullae and sheets of epidermal sloughing leaving behind red denuded areas are seen.

Drug Rash with Eosinophilia and Systemic Symptoms

Drug rash with eosinophilia and systemic symptoms (DRESS) is a potentially fatal hypersensitivity reaction to medication, most commonly anticonvulsants [10]. The incidence is between 1/1,000 to 1/10,000 exposures and it is thought to occur with higher frequencies in patients of African ancestry [11].

Although the etiology of DRESS is not understood completely, alteration in drug detoxification pathways and a causative role for human herpesvirus 6 have been proposed [12,13]. DRESS is most commonly caused by the aromatic anticonvulsants, including phenobarbital, phenytoin, and carbamazepine. Of note, these drugs may cross-react. Other common

causes include allopurinol, sulfonamides, minocycline, and dapsone.

In contrast to other drug reactions, DRESS may develop as late as 4 to 6 weeks after the offending medication has been introduced. DRESS has even been reported to occur more than 1 year after initiating allopurinol. The rash is usually morbilliform, though erythroderma, pustules, vesicles, and purpuric areas may also be present. High fever and edema of the face are hallmarks of this entity. Systemic involvement may include pharyngitis, lymphadenopathy, hepatosplenomegaly, peripheral eosinophilia, abnormal liver function tests, arthralgias, pulmonary infiltrates, and interstitial nephritis. Allopurinol and minocycline are associated with severe DRESS, the former frequently causing renal failure, and the latter causing pneumonitis [14]. Circulating atypical lymphocytes may also be present [11]. High eosinophil count and multiple medical comorbidities were poor prognostic factors in one series of 30 patients with DRESS [15]. Another study found that vitamin D deficiency was common among patients with DRESS, and that myocarditis is an underdiagnosed systemic manifestation, which may be detected by cardioselective biomarkers, echo, or cardiac MRI [16].

The differential diagnosis includes AGEP, SJS, TEN, Kawasaki's disease, and the hypereosinophilic syndrome. Histopathology of skin biopsies taken from patients with DRESS is variable and therefore not diagnostic [15]. The history of recent initiation of a suspect drug, the presence of atypical lymphocytes, peripheral eosinophilia, increased liver function tests, abnormal serum creatinine or urinalyses, and cutaneous eruption as described above, especially with facial edema, suggest the diagnosis of DRESS.

The most effective treatment is prompt diagnosis and cessation of the offending drug. Antipyretics may be used to treat the fever but they have no impact on disease outcome. Multiple independent case reports have suggested that systemic corticosteroid therapy may halt internal disease progression. Additionally, the disease has been reported to recur upon stopping corticosteroid treatment too soon. This has led many authorities to suggest treatment with systemic corticosteroids when there is internal involvement. However, no case control or randomized controlled trial data are available [17]. Thus, primary and secondary prevention of DRESS is of utmost importance. One must have knowledge of the most common causative drugs and an understanding of the cross-reactivity among the aromatic hydrocarbons. Mortality rates up to 10% have been reported and are primarily due to fulminant hepatitis.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP), also known as toxic pustuloderma [18] or pustular drug rash [19] is a very rare drug reaction that presents with fever, leukocytosis, and multiple pustules on a background of generalized erythema. There appears to be no sexual predilection and AGEP may occur at any age. Incidence rates have been estimated at 1 to 5 cases per million per year [20].

Drugs are responsible for at least 90% of AGEP cases. In a report of 97 cases from Europe, aminopenicillins (odds ratio [OR] = 23), macrolides (OR = 11), quinolones (OR = 33), hydroxychloroquine (OR = 39), calcium channel blockers (OR = 15), anticonvulsants (OR = 8), and corticosteroids (OR = 12) were the most common causative agents [21]. More recently, spider bites have been reported as triggers [22]. Patch testing with the offending agent is frequently positive reflecting the dominant role of T cells in the disorder.

The eruption is frequently sudden in onset and the majority of cases appear within 24 hours to several days of exposure to the offending agent. A fever of more than 38°C is followed by the appearance of tiny nonfollicular pustules on a background of generalized erythema and edema. Petechiae, purpura, vesicles, or target lesions may be present, and oral lesions may be observed in 20% of patients. The face and intertriginous areas are the most common presenting locations. Neutrophilia occurs in 90% and eosinophilia in 30% of patients. Liver function tests are usually normal and there is typically no systemic involvement, but lymphadenopathy is sometimes seen. The differential diagnosis includes pustular psoriasis, subcorneal pustular dermatosis, DRESS, and in severe cases, TEN. An acute onset and clinical history of a new drug favors AGEP over pustular psoriasis, whereas DRESS and TEN exhibit systemic involvement.

Discontinuation of the causative drug is the definitive treatment. Once the diagnosis is made and the causative drug is stopped, the pustules will resolve in less than 15 days with desquamation, and prognosis is excellent. Antipyretics may be used for symptomatic treatment of the fever and topical steroids may be used for symptomatic treatment of the rash, although neither will hasten the resolution of the eruption.

EXFOLIATIVE ERYTHRODERMA

Erythroderma (Fig. 195.4) is a rare, life-threatening skin condition characterized by erythema involving at least 90% of the body surface area with variable degrees of scaling [23–25]. While age at presentation varies with the underlying cause, patients are typically over 40 or 45 years. Male to female ratio and reported incidence are also variable, and there is no racial predilection [25–27].

The causes of erythroderma may be categorized into preexisting skin conditions (psoriasis, atopic dermatitis, contact dermatitis, and seborrheic dermatitis), drug reactions, malignancy, skin infections and infestations, and idiopathic etiology [23,25,27]. Over 60 topical and systemic medications have been implicated in erythroderma, including ACE inhibitors, anticonvulsants, penicillin, vancomycin, antifungals, and barbiturates [26,27]. Leukemias and lymphomas constitute up to 40% of malignancy-related erythrodermas. Cutaneous T cell lymphoma (CTCL) and Sezary syndrome represent most of these cases. Primary blood vessel malignancy and solid organ cancers are also reported in association with erythroderma [27]. SSSS, HIV seroconversion, superficial dermatophyte and candidal infections, scabies infestation, lupus erythematosus, sarcoidosis,

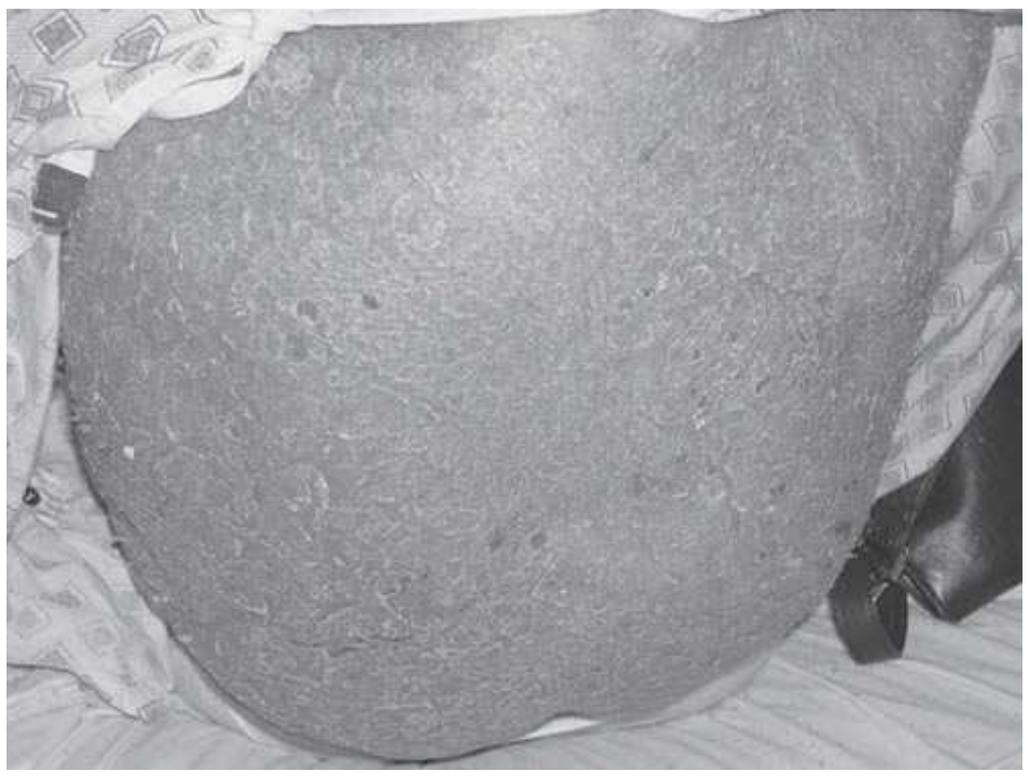

FIGURE 195.4. Exfoliative erythroderma. Widespread red blanchable erythema with scale.

and mastocytosis may rarely cause erythroderma as well. Up to 46% of cases have no identifiable trigger [23,26].

Varying degrees of scaling, which often begin at flexural surfaces, follow intense widespread erythema within 2 to 6 days. Erythroderma associated with psoriasis and atopic dermatitis has a more indolent course than the more rapidly progressive form linked to malignancy, drugs, and SSSS [26]. Along with intense erythema, patients may have fever, hyperkeratosis of the palms and soles, nail dystrophy, cheilitis, alopecia, edema of the face and legs, dermatopathic lymphadenopathy, hepatomegaly, and splenomegaly [25,26].

Erythrodermic patients have dramatic disturbances in the body's regulatory mechanisms. Increased cutaneous blood flow results in exaggerated heat and fluid losses with a compensatory increase in the body's basal metabolic rate. This, in conjunction with the shedding of 20 to 30 g per day of proteinaceous scale, can result in a hypoalbuminemia that exacerbates edema and nutritional deficits [26,27]. Complications include electrolyte imbalance, dehydration, high output cardiac failure, and secondary infections.

Identification of the underlying trigger is important in the evaluation and management of erythrodermic patients. Early examination of the skin with corroborating evidence from skin biopsy may be helpful in establishing the etiology, but in the majority of adult cases, the underlying dermatosis is obscured by widespread erythema and scaling. Skin biopsy has recently been shown to be more useful in detecting some underlying triggers for infantile and neonatal cases of erythroderma [28].

Erythroderma should be managed as a dermatologic emergency in the inpatient setting. Initial treatment, regardless of the underlying cause, consists of temperature regulation, hemodynamic support and monitoring, and skin care. Topical therapies include low-to-mid potency corticosteroids such as triamcinolone 0.025% to 0.1% cream under wet dressings. Tap water soaked gauze dressings may be changed every 2 to 3 hours, and tepid baths may provide additional relief. As the skin condition improves, emollients can be substituted for corticosteroids. Systemic corticosteroids can be helpful, but must be used with caution in atopic dermatitis and are contraindicated in infection and psoriasis. Additional therapy is targeted at the triggering disease and may include systemic retinoids, cyclosporine, or methotrexate in the case of psoriasis, and psoralen with UVA phototherapy in the case of CTCL [26,27]. Regardless of the underlying cause, relapses of erythroderma are common. Mortality rates range from 4.6% to 64% and are influenced by advanced age and comorbidities [25].

INFECTIONS

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is an acute febrile illness caused by toxin-producing strains of *Staphylococcus aureus*, presenting with fever, rash, and hypotension and often progressing to multiorgan failure [29]. A similar syndrome caused by *Streptococcus pyogenes* has also been described, known as streptococcal toxic shock syndrome (STSS) [30]. TSS is rare and more often seen in young women (yearly incidence of 1/100,000 women of reproductive age) than men, most likely due to its association with tampon use. Predisposing factors for TSS include menstruation, recent childbirth or surgery, burn wounds, intravenous drug use, pneumonia, and influenza. STSS has an estimated yearly incidence of 10 cases/100,000 population and shows no gender predilection [29]. Pathophysiology of both entities involves massive release of cytokines due to bacterial toxins acting as superantigens.

Both TSS and STSS present with high fever, headache, nausea and vomiting, and myalgias and arthralgias. Hypotension, metabolic acidosis, acute renal failure, elevated transaminases, thrombocytopenia, leukocytosis, disseminated intravascular coagulation, cardiomyopathy, and acute respiratory distress syndrome (ARDS) are often seen. Most patients with TSS do not have an obvious localized *S. aureus* infection. In contrast, 80% of patients with STSS have a clinically evident painful streptococcal soft tissue infection, often necrotizing fasciitis, usually of an extremity [29].

Skin findings are especially prominent in TSS, which classically presents with generalized macular (sunburn-like) erythema, but a scarlatiniform rash with accentuation of the flexures can also be seen. Erythema of the palms and soles, conjunctivae, and mucous membranes is also observed. The patient may develop a bright red "strawberry" tongue. The eruption is followed 1 to 2 weeks later by desquamation, especially of the palms and soles.

The differential diagnosis includes Rocky Mountain spotted fever, meningococcemia, Kawasaki's disease, SSSS, scarlet fever, or a medication hypersensitivity reaction. Blood cultures are positive in 60% of cases of STSS, less often (< 15%) in TSS [29]. Diagnosis is on clinical grounds and requires four major criteria (fever > 38.9°C, diffuse macular erythroderma, desquamation 1 to 2 weeks later, hypotension, and poor peripheral perfusion) and at least three minor criteria (vomiting or diarrhea; severe myalgia or CPK twice normal; hyperemic mucous membranes; elevated urea or creatinine; elevated bilirubin, ALT, or AST; platelets $< 100 \times 10^9$/L; and disorientation or altered consciousness). TSS also has a specific T cell signature with early depletion of the V beta 2 subset followed by massive expansion, which can aid in early diagnosis [31]. Skin biopsy showing a neutrophilic and eosinophilic perivascular and interstitial infiltrate with scattered necrotic keratinocytes can be helpful.

Treatment is with supportive care (intravenous fluids and vasopressors), penicillinase-resistant antibiotics, and intravenous immunoglobulin (IVIG) or fresh frozen plasma (FFP). Nafcillin 1 to 2 g intravenously every 4 hours is the first line antibiotic for TSS and clindamycin 600 to 900 mg intravenously every 8 hours for STSS. As cases of TSS due to methicillin-resistant *S. aureus* (MRSA) are increasing in frequency, treatment with vancomycin (1 to 2 g IV every 24 hours) may sometimes be necessary [32]. In addition, prompt surgical exploration and drainage of suspected deep tissue infections is critical in cases of STSS in which necrotizing fasciitis may be present.

In one study of IVIG in STSS, 30 day survival improved from 34% to 67% and in the only randomized placebo controlled study of treatments for STSS, IVIG decreased mortality by 3.6-fold [33]. TSS has a case fatality rate of less than 5%, whereas mortality in STSS ranges from 30% to 70%, and significant morbidity, including renal failure, amputation, or hysterectomy may also occur [29,30].

Cellulitis and Erysipelas

Cellulitis is an acute bacterial infection of the skin and subcutaneous tissues. Erysipelas is a superficial form of cellulitis that is more indurated and well demarcated than other forms of cellulitis, in which the border between involved and uninvolved skin is indistinct. Cellulitis is common and more frequently affects men than women. The lower extremities are most often involved (73% of cases), followed by the upper extremities (19%), and head and neck (7%) [34].

Cellulitis is usually caused by group A beta-hemolytic streptococci or *S. aureus*, including MRSA [35], although it may also be caused by Group B streptococci, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and other bacteria, in

certain settings. Erysipelas is almost always caused by Group A streptococci. Predisposing factors for cellulitis include venous stasis disease, lymphedema, lower extremity ulceration, tinea pedis, and obesity. Bacteria on the skin surface enter through breaks in the skin and proliferate in the dermis and subcutaneous tissues, causing inflammation.

Patients with cellulitis present with erythema, swelling, warmth, and tenderness of a poorly demarcated area, usually on the leg, often in the setting of lower extremity swelling or dermatitis. If a line is drawn around the involved area, the area of redness is often seen to spread outward over hours to days. Patients frequently have tender local lymphadenopathy and/or lymphangitis. Fever or myalgias are sometimes present. In erysipelas, the skin is bright red and the borders are elevated and sharply demarcated from the uninvolved skin.

Cellulitis has a broad differential diagnosis, including contact dermatitis, superficial thrombophlebitis, deep venous thrombosis, necrotizing fasciitis, lipodermatosclerosis, and insect bites or stings [36,37]. One of the most commonly confused entities is simple stasis dermatitis, which is usually bilateral with scaling and hyperpigmentation of the distal lower extremities in addition to erythema and swelling. It is usually not tender unless ulceration is present.

Diagnosis of cellulitis and erysipelas is generally on clinical grounds. Blood cultures are of low yield (4% positive) unless the patient has signs of sepsis, and tissue cultures from needle aspirates are positive in only 10% to 20% of cases [38]. However, if the patient has an active ulcer, this may be cultured. Radiographic studies are usually unnecessary, although plain films or computed tomography (CT) may be of value to evaluate underlying osteomyelitis, and magnetic resonance imaging (MRI) may be used to differentiate cellulitis from necrotizing fasciitis [36]. If necrotizing fasciitis is strongly suspected, surgical debridement and intravenous antibiotics should be initiated immediately without waiting for radiologic or microbiologic studies.

Treatment of cellulitis is directed at the most likely bacterial causes, which are Streptococci and *S. aureus*. Initial treatment of the hospitalized patient is with beta-lactamase-resistant penicillins or cephalosporins such as cefazolin 1 g IV every 6 hours, nafcillin 1 to 1.5 g IV every 4 to 6 hours, or ceftriaxone 1 g IV every 24 hours. If MRSA is suspected, treatment is with vancomycin 1 to 2 g IV every 24 hours. As the cellulitis begins to resolve and the patient becomes afebrile, the patient may be converted to oral dicloxacillin or cephalexin 500 mg every 6 hours, for a total course of 7 to 14 days of antibiotics [36].

Local treatment of a cellulitic limb with elevation to reduce swelling and saline dressings to any open wounds may be helpful. Prognosis of patients with uncomplicated cellulitis is excellent but recurrences are common. Treatment of underlying tinea pedis with topical azole antifungals and of venous stasis or lymphedema with compression hosiery can help prevent recurrences [36].

Necrotizing Fasciitis

Necrotizing fasciitis (NF) is a rapidly progressive infection involving the subcutis and fascia that typically occurs in the elderly, diabetics, alcohol abusers, and those with chronic cardiac disease or peripheral vascular disease. It is increasing in frequency among young, previously healthy individuals. NF may occur *de novo*, after surgery, or after penetration or even blunt trauma. Injection drug use is not an infrequent cause of NF [39]. The extremity is the usual site of involvement. When NF originates in the scrotum, it is known as Fournier's gangrene. Most cases result from a polymicrobial infection. Pathogens may include Streptococci, *S. aureus*, enterococci, *Escherichia coli, Pseudomonas*, *Bacteroides, and* Clostridium *spp*. Community acquired MRSA has been reported more recently [40]. Invasive Group A *Streptococcus* is implicated in previously healthy patients. Other less frequent pathogens include *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, and *Vibrio vulnificus, Haemophilus influenzae* type b.

The skin is initially shiny, erythematous, hot, tender, swollen, and tense. Pain is out of proportion to physical findings. Within 24 to 36 hours, skin color changes from red to dusky gray-blue, and bullae may develop. Deeper soft tissue may feel firm. With the destruction of cutaneous nerves, skin becomes anesthetic. The area becomes gangrenous by the fourth or fifth day, and patients appear toxic with fever, chills, tachycardia, shock, and leukocytosis.

NF may be difficult to differentiate from cellulitis, especially early in the course of disease. Features that suggest NF include: severe pain which may be out of proportion to physical findings, anesthesia of involved skin, rapid spread, edema and bulla formation, associated varicella infection, signs of shock, elevated creatine phosphokinase level, or NSAID use. NSAID use is implicated in disease progression through attenuation of signs and symptoms of inflammation that leads to a delay of diagnosis and treatment. MRI may help to discern extent of involvement. A newer tool called the laboratory risk indicator for necrotizing fasciitis uses a scoring system based on C-reactive protein, total white cell count, hemoglobin, sodium, creatinine, and glucose levels to help distinguish between necrotizing soft tissue infections and non-necrotizing infections, and in one retrospective study, was noted to predict mortality and amputation rate [41].

Early fasciotomy and immediate intravenous antimicrobial therapy based on initial Gram stain are crucial. Initial therapy usually involves a beta-lactam/beta-lactamase inhibitor. Hyperbaric oxygen therapy for anaerobic gram negative infection is controversial. Supportive care and attention to nutrition are important in optimizing postoperative wound healing. Even with early treatment, mortality may be between 20% and 40%. Poor prognostic factors include age over 50, diabetes, arteriosclerosis, delay of more than 7 days in diagnosis and surgical intervention, and infection involving the trunk rather than the extremity [42]. Other factors associated with mortality include STSS and immunocompromised state [39,43].

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a blistering, desquamative skin condition caused by the exfoliative toxins of *S. aureus*. Infants and young children are the most commonly affected, likely due to their immature immune and renal function, resulting in a lack of antitoxin antibodies and accumulation of exfoliative toxin. A few cases have been reported in adults who generally have underlying renal impairment or immunosuppression [44,45].

Two toxins, ETA and ETB, have been detected in human disease, with the majority caused by ETA. These toxins bind to and cleave desmoglein-1, a desmosomal protein in the superficial epidermis critical for binding between keratinocytes. Cleavage of this protein causes separation between keratinocytes in the upper layers of the epidermis and also of the superficial epidermis from deeper layers, with resulting fragile blisters and denuded skin [44,45].

In the localized form of SSSS, bullous impetigo, *S. aureus* enters the skin through a break or tear and elaborates exfoliative toxin that results in the development of blisters. Further spread is prevented by antibodies to the toxin. In generalized SSSS, the focus of infection is at a distant site, such as an abscess, pneumonia, osteomyelitis, or endocarditis. Frequently, however, a focus of infection is not found. A lack of protective antibodies

allows the toxin to reach the epidermis by hematogenous spread and cause widespread skin disease [44–46].

Whereas bullous impetigo has no associated systemic symptoms, generalized SSSS is associated with a prodrome of fever, malaise, and generalized erythema. This is followed by the formation of large blisters with clear or purulent fluid that easily rupture, leaving extensive areas of denuded skin. The degree of skin involvement may vary from focal blistering to entire body exfoliation. Significant pain and tenderness, hypothermia, fluid losses, secondary infection with *Pseudomonas* and other species, bacteremia, and sepsis may complicate the disease course [44,45].

SSSS should be considered for any presentation of fever and diffuse skin erythema. While the main differential diagnosis is toxic epidermal necrolysis, other conditions to consider include pemphigus foliaceus, scalding or chemical burns, GVHD, and epidermolysis bullosa. A thorough evaluation should include determination of the degree of denudation, identification of the source of infection, determination of fluid status, and a search for signs of secondary infection. Culture and Gram stain of the skin and focus of infection may identify *S. aureus*, but alone do not confirm the diagnosis of SSSS. Enzyme-linked immunosorbent assay (ELISA) can detect production of exotoxin from isolated *S. aureus* species, but should be used as confirmation of SSSS only, as false negatives can easily result if the pathogenic strain of bacteria is not detected on culture. Blood cultures are frequently positive in adults with SSSS [44,45].

Skin biopsy is the most useful diagnostic test, since it further distinguishes between SSSS and TEN. SSSS shows cleavage in the mid-epidermis with minimal associated inflammation. In TEN, cleavage occurs at the dermo-epidermal junction and there is cellular necrosis of the epidermis. TEN can also be distinguished clinically by the presence of mucosal involvement, a finding that is not seen in SSSS. Pemphigus foliaceus, an autoimmune blistering disorder caused by autoantibodies against desmoglein-1, can be difficult to distinguish both clinically and by routine histology [44,45]. Direct immunofluorescence will demonstrate anti-desmoglein antibodies in the epidermis of pemphigus foliaceus patients [47].

Treatment of generalized SSSS is with intravenous antibiotics targeting penicillin-resistant *S. aureus*. Aminoglycosides may be added if there are signs of secondary infection. Analgesia, fluid resuscitation, and wound care are other key elements of treatment. Use of steroids is contraindicated [44,45].

Exfoliation continues for 24 to 48 hours after institution of appropriate antibiotics. MRSA must be considered in any patient not responding to therapy after this time. Although the disease is rarely fatal in children, mortality in adults, even with treatment, is upward of 50% to 60%, when there are serious underlying medical conditions [44,45].

Meningococcemia

Neisseria meningitidis is a major cause of meningitis and sepsis in the United States, with an annual incidence of approximately 1 in 100,000. Meningococcal disease is often rapidly fatal due to shock and multiorgan failure. The majority of cases occur in winter and early spring. Infants and teenagers have the highest rates of infection. Meningococcal disease often occurs in localized outbreaks such as in schools or military barracks [48]. Most affected patients are previously healthy, but those with HIV, immunoglobulin deficiencies, asplenia, or inherited and acquired deficiencies of terminal complement components C5–C9 are at increased risk [48,49].

N. meningitidis is an aerobic gram positive diplococcus that only infects humans. Thirteen serotypes have been identified, of which groups A, B, C, Y, and W-135 are the major pathogens. A vaccine against types A, C, Y, and W-135 is in use for high-risk individuals. The bacteria inhabit the respiratory mucosa and are spread person to person through respiratory secretions. They possess virulence factors that allow invasion through the respiratory epithelium and into the bloodstream. There, they damage endothelium directly and release lipopolysaccharide endotoxin, which provokes massive release of tumor necrosis factor alpha, interleukins-1 and –6, and interferon-gamma. These cytokines promote vascular permeability, hypotension, and eventually multiorgan failure and disseminated intravascular coagulation [48,49].

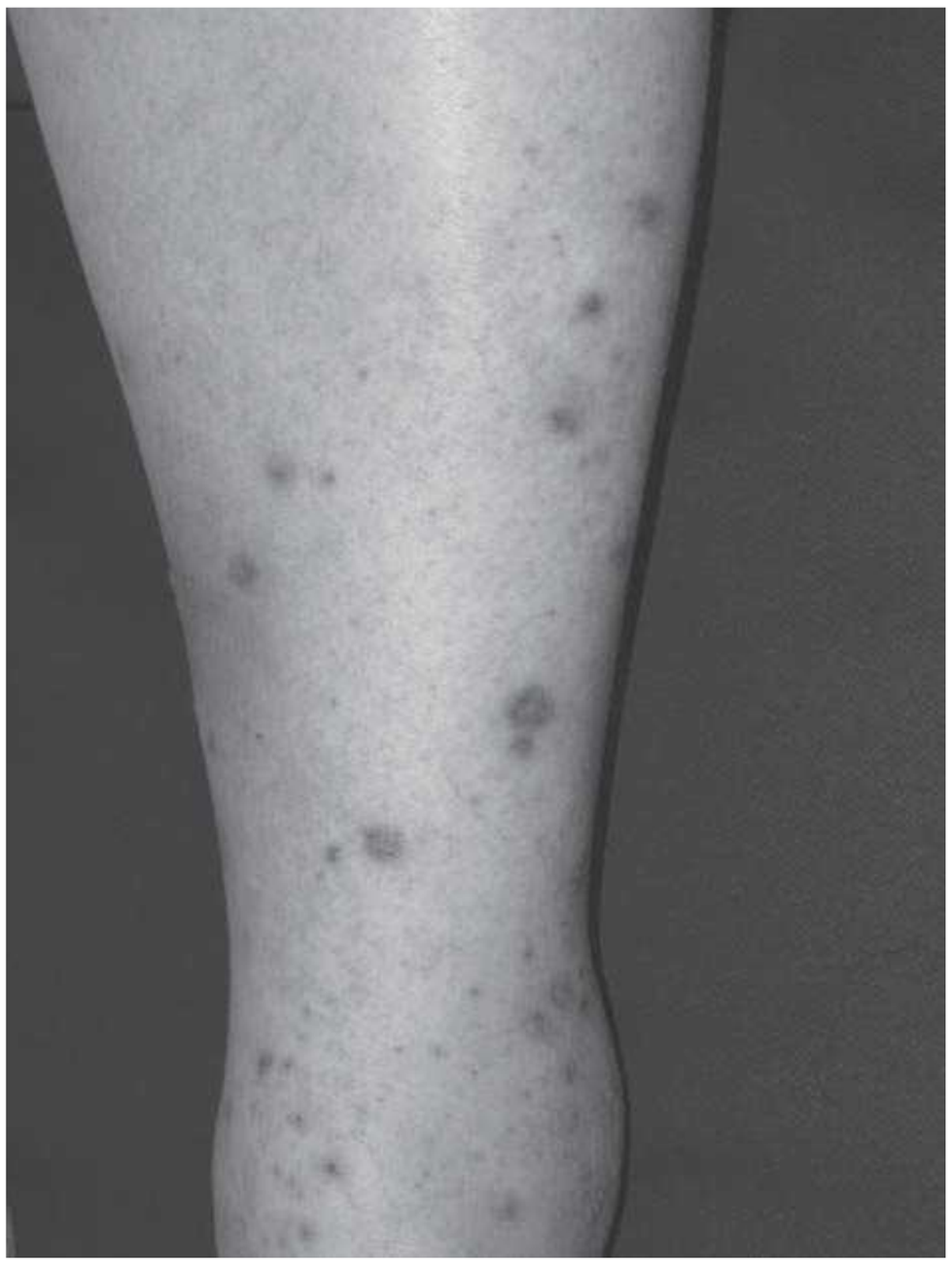

FIGURE 195.5. Meningococcemia. Purpuric papules and plaques, some of which have a dusky or gunmetal gray center.

Meningococcal disease may present in mild cases as a viral syndrome with fever, headache, nausea, vomiting, and arthralgias, but in fulminant cases, patients are severely ill with high fever, hypotension, and a hemorrhagic rash. Half of the cases will have meningitis with headache, stiff neck, and photophobia. Cutaneous findings are prominent in as many as 60% of patients with meningococcemia, with petechiae or purpura beginning at points of pressure on the trunk and extremities, but spreading to involve any body area. Urticarial and maculopapular lesions may also be observed early in the clinical course. As meningococcemia progresses, large areas of irregular gunmetal gray hemorrhage and necrosis may develop (Fig. 195.5) due to disseminated intravascular coagulation. In 10% to 20% of children with meningococcemia, purpura fulminans in combination with multiorgan failure and adrenal hemorrhage, the Waterhouse–Friderichsen syndrome, may occur [50].

The differential diagnosis of meningococcemia includes Rocky Mountain spotted fever, leukocytoclastic vasculitis, toxic shock syndrome, erythema multiforme, and other forms of bacterial sepsis. Diagnosis is usually based on blood or cerebrospinal fluid cultures, and in cases of meningococcal meningitis, gram staining of CSF is up to 90% sensitive. Newer polymerase chain reaction (PCR) tests for meningococcus are available, including the IS-1106, nspA, and ctrA TaqMan tests

[50,51]. Because meningococcal sepsis progresses rapidly and has a case fatality rate of up to 40%, treatment should never be delayed pending diagnosis.

Prompt treatment with an appropriate antibiotic is critical in treating meningococcal disease. First line treatment in adults 18 to 50 years of age is a broad-spectrum cephalosporin, such as ceftriaxone (2 g IV q12 hours). In adults over 50 years of age, ampicillin is given concomitantly. Once the diagnosis of meningococcemia is confirmed, patients in the United States may be switched to penicillin G (4 million units IV Q 4 hours), as penicillin-resistant strains have not been identified there [50]. Intensive supportive care with intravenous fluids, pressors, and ventilatory support is usually needed. Prognosis for untreated cases is very poor, with 70% dying before antibiotics were available. Overall case fatality of meningococcal disease is now around 10%, though it remains 40% for those with sepsis. Up to 19% of survivors have severe sequelae such as deafness or loss of a limb [48].

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is a life-threatening tick-borne febrile illness caused by the intracellular pathogen, *Rickettsia rickettsi*. Despite its name, RMSF is most commonly reported in the Southeast to Midwest states. Cases occur most often in the summer months, when humans are most likely to be exposed to ticks. RMSF is a rare disease, with an annual incidence of 2.2 cases per million [52]. The disease is most common in children, due to the relatively large amount of time they spend outdoors, where they are exposed to ticks.

RMSF is caused by *R. rickettsi*, a pleomorphic coccobacillary obligate intracellular parasite, which is transmitted to humans by the American dog tick (*Dermacentor variabilis*) in the Eastern United States and the wood tick (*Dermacentor andersoni*) in the mountain West.

R. rickettsi infects vascular endothelium and smooth muscle cells where it can replicate and spread to other cells, causing vascular and tissue injury. Vasculitis may occur in the gastrointestinal tract, lungs, kidneys, liver, heart, brain, and skin, leading to multiorgan failure. In addition, *R. rickettsi* promotes the coagulation cascade, leading to hypercoagulability and thrombocytopenia.

Most patients with RMSF present within 14 days of a tick bite with fever and severe headache. Rash usually occurs 2 to 5 days later. Roughly half of all patients will present with the classic triad of fever, rash, and headache. The rash of RMSF is initially blanching pink to red macules on the wrists and ankles, spreading to the palms and soles and then to the arms, legs, and trunk. The face is usually spared. Over several days, the rash becomes purpuric with areas of hemorrhage and necrosis [53]. In addition to fever and headache, patients frequently present with abdominal pain, nausea and vomiting, myalgias, and shortness of breath. Respiratory failure, myocardial edema, renal failure, liver dysfunction, and altered mental status may occur [54].

The differential diagnosis of RMSF includes other febrile illnesses with rash, such as ehrlichiosis, meningococcemia, toxic shock syndrome, measles, drug fever, idiopathic thrombocytopenic purpura, and various viral syndromes. In cases where no rash occurs, the differential diagnosis would include appendicitis, gastroenteritis, and other causes of acute abdomen. Several diagnostic tests are helpful, but in no case should treatment be delayed pending results once RMSF is suspected. The indirect fluorescent antibody test for *R. rickettsi* is 94% sensitive and specific but requires 7 to 14 days to become positive. Skin biopsy shows a lymphohistiocytic vasculitis with extravasation of red blood cells and occasional fibrin thrombi. *R. rickettsi* may be identified intracellularly by Giemsa staining. Nonspecific laboratory findings include thrombocytopenia and elevated transaminases.

Treatment of RMSF is with doxycycline 100 mg twice daily (or 3 mg/kg of body weight, whichever is higher) for at least 7 days, given orally for outpatients and intravenously for hospitalized patients. Doxycycline should be used even in children (at a dose of 4.4 mg/kg per day divided into BID doses), as the risk of tooth staining has been shown to be quite low for short-term therapy. This regimen will cover other tick-borne illnesses such as Lyme disease and ehrlichiosis, as well as RMSF. Chloramphenicol (at a dose of 50 to 75 mg per kg per day divided into four doses) is an alternative choice for pregnant women and patients with documented allergy to doxycycline, but is reportedly less effective [55]. Treatment should be continued until the patient has been afebrile for 2 to 3 days.

Case fatality rates range from 0.6% to 9%, with worse prognosis in older patients. Untreated RMSF has a mortality of 25%, whereas patients receiving appropriate treatment within 5 days of symptom onset have a mortality of 5% [52].

Disseminated Herpes Simplex Virus Infection

Herpes simplex virus (HSV), a member of the human herpes virus family, is a common cause of dermatologic disease. HSV-1 and HSV-2 have seroprevalence rates as high as 80% and 25% of U.S. adults respectively [56].

Infection is spread by close physical contact of mucous membranes or open skin with infected fluids or skin that is actively shedding virus. After initial infection, the virus remains latent in the dorsal root ganglion. Reactivation may be triggered by stress, illness, trauma (such as from intubation), intense UV exposure, and pregnancy. Grouped vesicles on an erythematous base, often with associated pain or pruritus, appear with reactivation. Rupture of vesicles leaves characteristic punched-out ulcers with scalloped edges [56,57].

Infection in immunocompetent patients is self-limited [58]. Immunocompromised patients (HIV, malignancy, medications, or pregnancy) have more frequent, more severe reactivations and there is an increased risk of disseminated cutaneous and visceral disease [56,58]. Reactivation of genital HSV in immunocompromised and pregnant individuals is associated with an increased risk of visceral dissemination and high mortality. Patients with disrupted skin secondary to eczema, TEN, burns or other conditions, are at risk for disseminated cutaneous disease known as Kaposi's varicelliform eruption or eczema herpeticum [56].

Patients with vesicular eruptions should be examined carefully for clustered lesions or erosions suspicious of HSV. A high index of suspicion is essential. The differential diagnosis includes herpes zoster, varicella, contact dermatitis, bullous impetigo, and other causes of vesiculation of the skin. Confirmatory tests include Tzanck smear, direct fluorescent antibody (DFA), viral culture, PCR, and ELISA. All studies are most sensitive when performed on vesicles less than 48 hours old. DFA and culture should be performed together to increase sensitivity from approximately 50% for each alone, to almost 80% [59]. PCR is the most sensitive test, but it is not always available.

Although there are no controlled studies for treatment of disseminated disease and no evidence that treatment decreases mortality, intravenous acyclovir at 8 to 10 mg per kg every 8 hours for 7 to 10 days is generally employed [57]. The dose is adjusted for patients with renal insufficiency. Alternatives for acyclovir-resistant cases include foscarnet, vidarabine, and cidofovir [58]. Secondary bacterial infection may complicate the course of HSV infection and should be treated with appropriate antibiotic therapy.

Disseminated Herpes Zoster

Varicella zoster virus (VZV) causes both chicken pox (varicella), representing a primary infection, and shingles (zoster), a manifestation of reactivated latent infection. After initial exposure, the virus remains dormant in the dorsal root ganglion [60] or in cranial nerve root ganglia [61]. Medications, aging, malignancy, bone marrow transplant, HIV, and poor nutrition can affect immune status and thereby increase the risk of reactivation. Incidence is approximately 5 per 1,000 per year, with no sex predilection, but there is significantly higher occurrence in at-risk populations and the elderly. A vaccine that is 50% to 64% effective against zoster is now in clinical use, but is not universally administered [60].

Upon reactivation, VZV tracks along sensory nerves to affect a particular dermatome, most commonly the thoracic dermatome. A prodrome of pain, pruritus, and paresthesia in the affected dermatome is noted by up to half of the patients. This is followed by an eruption of erythematous macules and/or papules. Over 24 hours, the lesions begin to vesiculate, and over the next 48 to 72 hours, crust over. Pain is the most common symptom, present in 90% to 95% of patients. Prior to onset of skin lesions, involvement of the thoracic dermatome may be mistaken for acute coronary syndrome.

Immunocompromised hosts may have atypical presentations with unusual lesion morphology, distribution, greater ulceration, and dissemination. Disseminated disease, defined as more than 20 lesions outside the primary dermatome, may present with multiple contiguous or non-contiguous dermatomes. Visceral dissemination can involve the lung, liver, and brain [61], but even in immunocompromised hosts, visceral disease is a low likelihood [60]. Cases of VZV reactivation and visceral dissemination without cutaneous lesions have been rarely reported [60,62].

Uveitis, keratitis, corneal ulcers, and blindness may result from reactivation along the ophthalmic division of the trigeminal nerve. Myelitis or encephalitis may result in weakness and altered mental status. Rarely, motor nerves may be involved with resulting weakness [60].

Differential diagnosis includes HSV infections, bullous drug eruption, contact dermatitis, and erythema multiforme. Tzanck smear, direct fluorescent antibody, or viral culture should be performed if the diagnosis is in question. However, treatment should not be delayed pending results. Patients should be treated if they present within 1 week of onset of their lesions or if they still have any lesions that have not crusted over [61].

Oral acyclovir or valacyclovir is appropriate for healthy individuals who can take oral treatment and for uncomplicated cases in immunocompromised patients. The dosing regimen is 1 g of valacyclovir or 500 mg of famciclovir every 8 hours, or acyclovir 800 mg 5 times a day, with dose adjustment for renal insufficiency. The duration of treatment is 7 to 10 days. IV acyclovir is the treatment of choice in immunocompromised patients with ophthalmic, disseminated, or HIV-associated disease or those with significant comorbidities [60,61]. Acyclovir resistance is more prevalent in immunocompromised populations and should be suspected if new lesions are forming on acyclovir or a related drug (famciclovir, valacyclovir). Viral sensitivities should be checked in this setting. Resistant strains are treated with foscarnet, 180 mg per kg per day divided into two or three doses and renally adjusted [61]. CNS, ophthalmologic, or atypical cutaneous presentations should trigger neurology, ophthalmology, and dermatology consultation [60,61].

Disseminated Candidiasis

Systemic candidiasis may occur as candidemia or as an infection involving a single or multiple organs. It is the fourth most common cause of bloodstream infection in hospitalized patients, with *C. albicans* and *C. glabrata* comprising 70% to 80% of these cases [63]. Immunosuppression and granulocytopenia are important risk factors for candidemia. Patients at high risk include those with hematologic malignancies, those undergoing chemotherapy, and organ and stem cell transplant recipients. Other risk factors for systemic candidiasis include ICU stay, presence of a central venous catheter, parenteral nutrition, broad-spectrum antibiotics, severe trauma, burns, hemodialysis, abdominal surgery, and GI perforation.

Skin lesions are present in up to 35% of patients with systemic candidiasis [63,64]. The eruption appears as pink or violaceous, firm papules or nodules most commonly on the trunk and extremities, but can also involve the face [64]. The lesions are often purpuric, which may be due to concurrent thrombocytopenia or vascular damage from the candida [64]. Other presentations include hemorrhagic or necrotic lesions, pustules, and abscesses. The eyes, kidney, liver, heart, and meninges may also be affected by hematogenous spread of the organism.

Blood cultures are positive in only 50% to 60% of patients with disseminated candidiasis; therefore, biopsy of a skin lesion is a more sensitive approach in early diagnosis and should be submitted for both pathology and tissue culture. Histopathology demonstrates aggregates of hyphae and spores in the dermis. The 1–3 D-glucan detection assay, which was approved by the FDA in 2004, measures the level of glucan in the fungal cell wall and therefore detects fungi, including candida, with a high degree of sensitivity and specificity.

Treatment requires extended courses of a systemic antifungal, usually fluconazole, caspofungin, or less commonly amphotericin B. Intravenous micafungin is a newer agent for invasive candidiases, which was well tolerated in clinical trials [65]. Intravenous catheters should also be removed and replaced, as should other potential sources of infection. With a mortality rate of 30% to 40%, systemic candidiasis causes more fatalities than any other systemic mycosis [63].

BLISTERING DISEASES

Pemphigus vulgaris, paraneoplastic pemphigus, and bullous pemphigoid are autoimmune blistering disorders characterized by autoantibodies directed at cell–cell adhesion molecules or components of the basement membrane zone.

Pemphigus Vulgaris

Pemphigus vulgaris is a rare but potentially fatal bullous disorder that affects the skin and mucous membranes. The worldwide incidence is 0.76 to 5 per million population. However, the incidence is much higher in those of Jewish ancestry [66]. Pemphigus typically affects middle-aged or older individuals. Pemphigus is caused by autoantibodies against the desmosomal proteins, desmoglein 1 and 3, which are required to maintain cellular adhesion between keratinocytes in the epidermis.

Virtually all patients with pemphigus develop painful oral erosions, which are usually the presenting signs. Hoarseness and dysphagia may be a sign of pharyngeal and esophageal involvement, respectively. Cutaneous lesions develop in more than half of the patients, usually after the onset of oral erosions. Vesicles or bullae in pemphigus are fragile and rupture easily since blistering occurs within the epidermis. Consequently, it is more likely to encounter erosions rather than intact blisters on the skin. Blistering may be induced by rubbing intact, normal appearing skin near areas of blistering, a phenomenon known as the Nikolsky sign. Extensive loss of epidermal barrier function in pemphigus may be complicated further by secondary systemic bacterial infection and fluid loss.

TABLE 195.2

SUMMARY OF RECOMMENDATIONS BASED UPON RANDOMIZED CONTROLLED CLINICAL TRIALS FOR PEMPHIGUS VULGARIS

Intervention	Year	Study	No. of Patients	Findings	Reference
Oral prednisolone, high dose (120 mg/d) versus low dose (60 mg/d) regimens	1990	Prospective, randomized trial over 5 y	22	High dose regimen had no long-term benefit over low dose regimen in terms of frequency of relapse or incidence of complications	Ratnam et al. [67]
Adjuvant oral dexamethasone pulse therapy (300 mg pulses 3 d/mo) versus placebo in conjunction with conventional oral prednisolone (80 mg/d) and azathioprine sodium (3 mg/d)	2006	Multicenter, randomized, placebo-controlled trial	20	No benefit of oral dexamethasone pulse therapy given in addition to conventional treatment	Mentink et al. [68]
Comparison of four treatment regimens for pemphigus vulgaris: prednisolone alone, prednisolone plus azathioprine, prednisolone plus mycophenolate mofetil, and prednisolone plus intravenous cyclophosphamide pulse therapy	2007	Randomized, controlled open-label trial over 1 y	120 (30 pts/arm)	Efficacy of prednisolone is enhanced when combined with cytotoxic agent. Azathioprine was found to be the most efficacious cytotoxic drug to reduce steroid, followed by cyclophosphamide and mycophenolate mofetil.	Chams-Davatchi et al. [69]
Comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil	2006	Prospective, multicenter, randomized, non-blinded trial	33	Azathioprine and mycophenolate mofetil have similar efficacy, corticosteroid-sparing effects and safety profiles as adjuvant treatments.	Beissert S et al. [70]
High dose intravenous immunoglobulin (IVIG) over 5 consecutive days in patients relatively resistant to systemic steroids	2009	Multicenter, randomized, placebo-controlled, double-blind trial	61 (includes pemphigus foliaceus)	IVIG (400 mg/kg/day for 5 days) is safe and effective for relatively steroid resistant patients.	Amagai M et al. [71]
Dapsone versus placebo in patients already on conventional systemic steroids	2008	Multicenter, randomized, placebo-controlled, double-blind trial	19	"Trend to efficacy" of dapsone but not statistically significant.	Werth et al. [72]
Cyclosporine as adjuvant to systemic corticosteroids	2000	Concurrently randomized trial	29	Cyclosporine ineffective as adjuvant to corticosteroids.	Ioannides D et al. [73]

For patients with only oral disease, the differential diagnosis includes oral HSV, aphthous ulcers, oral lichen planus, and systemic lupus erythematosus. With cutaneous disease, further consideration should be given to bullous impetigo, bullous drug eruptions, and other autoimmune blistering disorders. Drug-induced pemphigus has been associated with the use of various medications, in particular penicillamine and captopril [66].

Diagnosis of pemphigus is made by routine histology, which demonstrates loss of cell–cell adhesion of keratinocytes (acantholysis) and retained attachment of basal cells to the basement membrane along the dermal-epidermal junction. Immunofluorescence of perilesional tissue shows intercellular deposits of IgG. Serum sent for indirect immunofluorescence or ELISA assays will demonstrate circulating antibodies, and titers in pemphigus usually correlate with disease activity [66].

Standard treatment of pemphigus is oral prednisone at 1 mg per kg per day. Studies of corticosteroid-sparing agents for pemphigus, including azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, and IVIG, are reviewed in Table 195.2 [67–73]. Plasmapheresis and rituximab have also been reported to be effective in case series. However, based on a Cochrane review [74], the optimal therapeutic strategy has not been established. Most patients require maintenance treatment for sustained remission. Prior to treatment with oral corticosteroids, most patients died within 5 years of disease onset. Current mortality rate is about 5% to 15%, mostly due to complications from immunosuppressive therapy such as sepsis [66].

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a variant of pemphigus associated with benign or malignant neoplasms. Most commonly associated conditions include non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease, thymoma,

sarcoma, and Waldenstrom's macroglobulinemia. Autoantibodies in paraneoplastic pemphigus are directed against a variety of proteins including desmogleins 1 and 3, Bullous Pemphigoid Antigen 230, as well as the plakin family of proteins [75].

The disease usually presents with a recalcitrant stomatitis involving the mouth and characteristically, the lips. Other mucous membranes, including the eyes, genitalia, nasopharynx, and esophagus, may be involved. Cutaneous lesions are polymorphic and may resemble pemphigus vulgaris, bullous pemphigoid, erythema multiforme, or lichen planus. Some patients develop bronchiolitis obliterans, which may be fatal as a result of respiratory failure [75].

Two thirds of patients diagnosed with paraneoplastic pemphigus have a known underlying neoplasm. In the other third, mucocutaneous disease precedes the diagnosis of an associated neoplasm, and these patients must be carefully followed. Severe, intractable stomatitis is a clue in differentiating paraneoplastic pemphigus from other bullous disorders.

Disease associated with benign neoplasms such as thymoma or Castleman's disease may improve or clear completely with treatment of the underlying condition. The course of disease and prognosis in malignancy-associated paraneoplastic pemphigus is poor. The stomatitis is often refractory to treatment with corticosteroids and immunosuppressants [75].

Bullous Pemphigoid

Bullous pemphigoid (BP) is a chronic subepidermal blistering disorder that usually affects the elderly. It has an incidence of 6 to 7 cases per million. It is usually not life-threatening but often requires long-term use of immunosuppressive agents, which can lead to morbidity and mortality.

Subepidermal blisters in BP result from autoantibodies directed against the hemidesmosomal proteins BP180 and BP230, which are located at the epidermal-dermal junction. BP may be induced by medications, the most common of which are penicillamine and furosemide. Other reported associations include captopril, bumetanide, phenacetin, amoxicillin, ciprofloxacin, potassium iodide, and gold [76].

BP has a variety of clinical manifestations, including a nonbullous prodromal phase characterized by severe pruritus, either alone or associated with excoriated eczematous or urticarial lesions. The bullous phase is characterized by tense vesicles and bullae on normal or erythematous skin. Unlike pemphigus, numerous blisters in bullous pemphigoid are found intact. The lesions are frequently symmetric and are most commonly found in flexural areas on the limbs, the lower trunk, and abdomen. The oral mucosa is involved in 10% to 30% of patients [76].

The differential diagnosis includes pemphigus, bullous lupus erythematosus, dermatitis herpetiformis, bullous erythema multiforme, cicatricial pemphigoid, linear IgA dermatosis, and epidermolysis bullosa acquisita. Diagnosis is made by skin biopsy from the edge of a blister, which shows a subepidermal blister with an eosinophil-rich dermal inflammatory infiltrate. Direct immunofluorescence of perilesional skin shows linear deposits of IgG and/or C3 along the basement membrane zone. Indirect immunofluorescence will detect circulating autoantibodies in 60% to 80% of patients [76].

Bullous pemphigoid has a tendency toward remission and can be controlled more easily than pemphigus. Treatment with high-potency topical corticosteroids may be effective with fewer side effects than the usually employed therapy with oral corticosteroids. Other immunosuppressive agents such as azathioprine, mycophenolate mofetil, cyclophosphamide, and methotrexate may be added for recalcitrant cases or for steroid sparing. The combination of nicotinamide and minocycline or tetracycline has been successful in small case series. Dapsone, IVIG, plasmapheresis, and extracorporeal photopheresis have all been reported to be effective as well.

VASCULAR DISORDERS

Cutaneous Vasculitis

Vasculitis is defined by inflammation of the blood vessel wall and may involve any sized vessel. Since this subject is covered in more depth in Chapter 196, the present discussion will focus on cutaneous findings. Vasculitis may be limited to the skin, or there may be multiorgan involvement involving most commonly the kidneys, the gastrointestinal tract, and/or the joints. It is important to recognize that skin involvement may be a sign of more serious internal organ involvement. The pathogenesis involves immune complex deposition in the affected vessel walls leading subsequent activation of complement. Vasculitis may primary, or secondary to infections (15% to 20%), medications (10% to 15%), malignancy (2% to 5%), or inflammatory disorders including connective tissue disease, inflammatory bowel disease, and others (15% to 20%) [77]. Commonly associated infections include *Streptococcal* and other bacterial acute respiratory infections, bacterial endocarditis, gonococcemia, chronic meningococcemia, hepatitis B and C, HIV, CMV, and mycobacteria. Implicated medications include antibiotics, allopurinol, thiazide diuretics, hydantoins, propylthiouracil, NSAIDs, and anti-TNF agents. Malignancies associated with vasculitis include lymphoproliferative, hematologic, and solid organ cancers. Among connective tissue diseases, systemic lupus erythematosus and rheumatoid arthritis are most likely to be complicated by cutaneous and systemic vasculitis. The underlying etiology may remain unidentified in up to 50% of patients [77].

Vasculitis affecting the skin may be a clue to involvement of other organs. Recognition of cutaneous morphologies associated with vasculitis allows for early recognition and classification of disease, timely workup and diagnosis, and prompt treatment. Cutaneous findings in vasculitis correlate with the size of vessels involved.

Cutaneous small vessel vasculitis includes Henoch-Schonlein purpura, urticarial vasculitis, septic vasculitis, and essential mixed cryoglobulinemia in which HCV may precipitate an immune response. The morphologic hallmark of small vessel vasculitis in the skin is palpable purpura. Red to purple, nonblanching macules and papules are concentrated over dependent areas of the skin such as the ankles and lower legs (Fig. 195.6), or over pressure areas such as the buttocks. There may be significant associated edema. Other morphologies include urticarial lesions, which are less evanescent than typical hives. The patient may have associated constitutional symptoms and arthralgias. Although most cases of cutaneous small vessel leukocytoclastic vasculitis affect only the skin, further consideration should be given to involvement of the renal, gastrointestinal, and central nervous system vasculature. The eruption typically resolves over weeks with hyperpigmentation. It is important to monitor for systemic disease, even after the cutaneous signs have resolved.

Polyarteritis nodosa, Wegener's granulomatosis, and Churg-Strauss syndrome are conditions in which there is inflammation of small and medium sized arteries. Mucocutaneous findings may be found in Churg-Strauss syndrome (55%) and Wegener's granulomatosis (40%). These conditions may present with painful subcutaneous nodules that often ulcerate, typically on the dependant areas such as the lower legs. Other mucocutaneous findings may include a necrotizing livedo reticularis, digital ischemia with gangrene, and oral ulcers. Palpable purpura, splinter hemorrhages, and pustules may also be

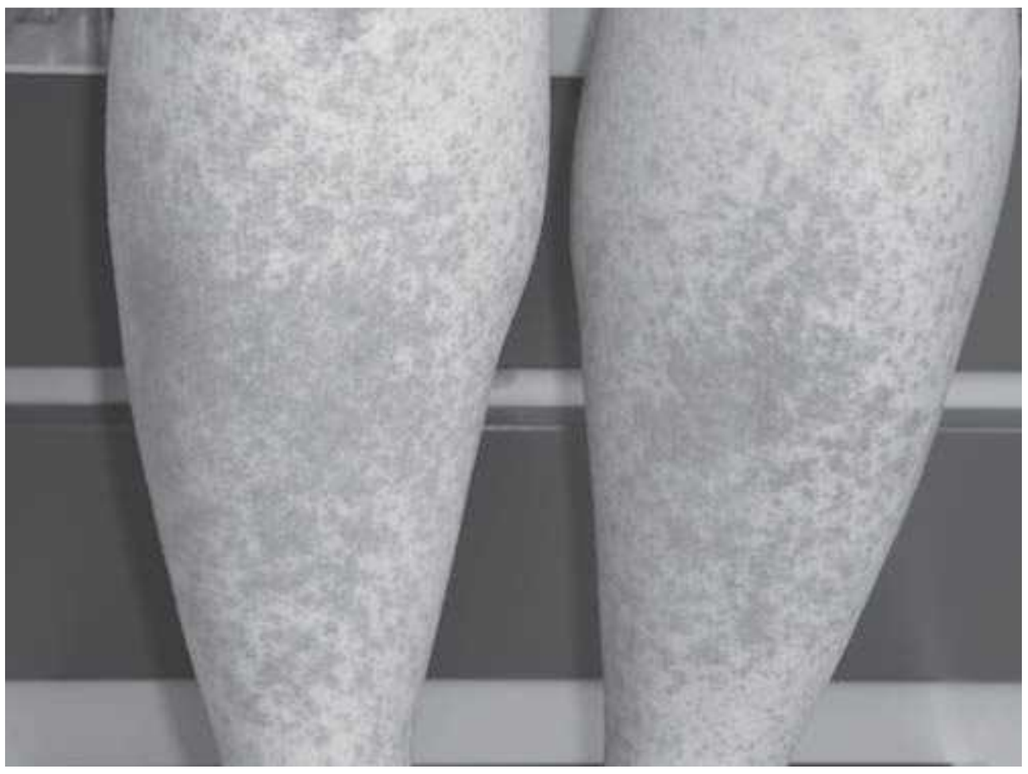

FIGURE 195.6. Vasculitis. Nonblanching, red to purple papules and plaques over the legs associated with edema.

present when there is concomitant small vessel disease. There may be associated constitutional symptoms, myalgias, and arthralgias. Peripheral sensorimotor neuropathy, cardiomyopathy or myocardial infarction, gastrointestinal symptoms and intestinal infarction, seizures, hemiplegia, and necrosis of major organs may also result from inflammation of larger vessels.

Disorders with large vessel vasculitis are usually diagnosed when bruits, asymmetric pulses, claudication, or neurologic deficits are present. Some patients also have cutaneous findings that serve as clues to underlying pathology. In giant cell arteritis (GCA), the temporal artery is tender, swollen, indurated, or pulseless. The tongue may be tender, atrophic, swollen, or cyanotic. Rarely, patients with GCA may have tender nodules overlying other superficial arteries. In less than 20% of cases of Takayasu's arteritis, erythema nodosum-like nodules or pyoderma gangrenosum like ulcers may be present. Cutaneous findings, although present in 80% of patients, are nonspecific in Kawasaki's disease, a syndrome associated with coronary artery aneurysms in 12% of affected children. The eruption of Kawasaki's disease is polymorphous, and patients may present with macules, papules, wheals, targetoid plaques, papulovesicles, pustules, or a scarlatiniform eruption most commonly on the abdomen, groin, perineum, and buttocks. There is often desquamation of the fingertips and mucous membrane involvement may include conjunctival injection, dryness of the lips, erythema of the mouth, and prominent tongue papillae (strawberry tongue). Most patients have enlarged cervical lymph nodes and high fever.

Histopathologic evaluation is important for diagnosis and early lesions are most revealing on biopsy. Thus, timely consultation of the dermatology service is important. Along with determining size of vessel disease, microscopic evaluation of tissue vessels distinguishes inflammatory from noninflammatory vessel disease. Furthermore, immunofluorescence studies of sampled tissue may help confirm a diagnosis of IgA vasculitis associated with Henoch-Schonlein purpura.

It is important to consider coagulopathies and other occlusive vascular diseases in the differential diagnosis of vasculitis since the management of noninflammatory vessel disease differs from that of vasculitis. Purpura, livedo reticularis, ulcers, and necrosis are manifestations of coagulopathies such as immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), drug-induced thrombocytopenia, inherited platelet dysfunction, warfarin and heparin necrosis, disseminated intravascular coagulation (DIC), gammopathies, protein C and S deficiencies, and the antiphospholipid syndrome. In bland occlusive disorders in which vessels may be occluded by fibrin, cryoglobulins, or emboli, the purpura may be palpable as in leukocytoclastic vasculitis, so the clinical distinction is not always apparent.

Treatment is directed at the underlying etiology and preventing the progression of inflammation. It is always important to evaluate and treat any underlying cause, whether it is infection, malignancy, or drug. With early intervention, morbidity and mortality from vasculitis may be reduced. For disease limited to the skin, supportive care with rest, leg elevation, and analgesics is usually sufficient. NSAIDs, colchicine, dapsone, or prednisone are helpful for patients with recalcitrant or progressive skin disease. Severe intractable skin disease or involvement of organs other than the skin requires immunosuppressive therapy with high dose prednisone 1 to 2 mg per kg per day, sometimes with steroid sparing support from methotrexate, cyclosporine, azathioprine, or cyclophosphamide [77].

Purpura Fulminans

Purpura fulminans (PF) is characterized by extensive purpura and necrosis of the skin associated with fever, DIC, sepsis, and hypotension. PF is seen mostly in three clinical settings: acute infections, inherited or acquired coagulopathies, and idiopathic. Meningococcemia, in which 3% of cases develop PF, is the most commonly associated infection. Varicella and pneumococcal sepsis are less frequently associated and rare or isolated reports include *H. influenza* [78] and other organisms. Asplenism is a risk factor for infection associated with PF. PF in the newborn period is usually due to an inherited coagulopathy and results in high mortality. PF has also been reported in association with acquired coagulopathies seen in inflammatory bowel disease [79,80]. Idiopathic disease is the mildest variant [81–83].

The pathophysiology of PF depends on the underlying trigger. The common endpoint is that of extensive microvascular thrombosis that affects cutaneous and visceral blood supply. In meningococcemia, endotoxin results in release of cytokines and activation of coagulation pathways, and infection is associated with substantially decreased levels of protein C [81].

Initially in PF, there is pain and erythema in affected areas. Irregular areas of blue–black discoloration develop within the center of erythematous patches, and lesional skin becomes indurated. There is progression to hemorrhagic vesicles and bullae, and finally to tissue necrosis. Lesions associated with infection tend to involve distal parts first and spread proximally, while idiopathic and coagulopathy-associated disease may remain localized to the lower extremities. Idiopathic PF usually affects only the skin; however, other forms may result in widespread necrosis with multiorgan failure. Disease complications include scarring, secondary infection, digital or limb necrosis, and autoamputation [81–83].

Differential diagnosis of PF includes Henoch-Schonlein purpura and post-infectious thrombocytopenic purpura, although these are both associated with milder disease than seen in PF. The presence of DIC helps distinguish PF from other causes of cutaneous necrosis [82].

Early recognition of disease and underlying trigger is essential in this rapidly progressive condition. Appropriate antimicrobials are instituted for infection. Supportive care includes aggressive fluid resuscitation, electrolyte monitoring, and replacement of blood products. If deficient, protein C and antithrombin III may be replaced. Other treatment options include fresh frozen plasma, heparin, plasmapheresis, topical nitroglycerin (for local vasodilation), and recombinant tissue plasminogen activator [82]. Surgical consultation may be necessary for debridement and grafting.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APS) is characterized by a hypercoagulable state with venous or arterial thrombosis, recurrent fetal loss, thrombocytopenia, and elevated titers of the antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant, anti-β-2 glycoprotein I antibodies). Up to 2% of the normal population exhibits detectable titers of these antibodies and 0.2% have elevated titers. APS may be primary, or it may be seen in conjunction with systemic lupus erythematosus, malignancy, drugs, infection, or hematologic disease [84–86].

Cutaneous manifestations in APS, although highly variable, are common and often the presenting sign of disease. Therefore, recognition of these findings is essential for early diagnosis and prompt evaluation for more extensive disease. Skin lesions are thought to be a direct result of arterial or venous occlusion and subsequent ischemia. The most common finding is livedo reticularis or livedo racemosa, seen in up to 40% of patients, and up to 70% of patients who have systemic lupus. These present as a netlike pattern of dusky erythema often found on the upper or lower extremities; they are thought to be more common in cases with underlying arterial disease and are less often seen in veno-occlusive disease [87]. Other associated findings include cyanotic macules, ecchymoses and purpura, ulcerations of the ears, face, and legs, porcelain-white scars (atrophie blanche) at the ankles, thrombophlebitis, Raynaud's phenomenon, digital ischemia, and gangrene. Any major organ systems can be affected by thrombosis [84–86].

The differential diagnosis of APS includes other disorders with associated livedo reticularis and cutaneous necrosis including vasculitis, warfarin-induced skin necrosis (WISN), cholesterol emboli, and cryoglobulinemia. Similar to other vaso-occlusive disorders, APS shows bland thrombosis of small dermal vessels. APS is distinguished from other noninflammatory vaso-occlusive disorders by the presence of elevated antiphospholipid antibody titers [84,86]. Although cutaneous findings are common, they are not among the diagnostic criteria for APS, which require positive antibodies on two occasions at least 6 weeks apart in addition to a history of vascular thrombosis or pregnancy complications [88].

Both treatment and prophylaxis consist of anticoagulation. Some advocate the use of aspirin in those without a history of thrombosis or with superficial venous thrombosis only. Otherwise, long-term warfarin anticoagulation with an INR goal of 3 to 4 is recommended. Immunosuppressive agents and immunotherapy (plasmapheresis, intravenous immunoglobulin, cyclophosphamide) may help reduce antibody levels, but is likely to rebound once treatment is discontinued [84,86].

Warfarin-Induced Skin Necrosis

Warfarin-induced skin necrosis (WISN) is seen in 0.01% to 0.1% of individuals on warfarin, 3 to 10 days after starting therapy. Women are affected four times more frequently than men, and are most often middle-aged and obese. Three quarters of patients with WISN are being treated for deep venous thrombosis or pulmonary embolism. Atrial fibrillation, valve replacement, and arterial occlusion are disorders in which anticoagulation with warfarin less commonly results in WISN [89].

Although the pathophysiology of WISN is not understood completely, the generally accepted mechanism involves the imbalance between intrinsic procoagulant and anticoagulant factors created early on during warfarin therapy. Due to their short half-lives, anticoagulant protein C and factor VII are depleted before procoagulant factors II, IX, and X, and this results in an initial hypercoagulability that is thought to trigger onset of WISN [89]. Most individuals on warfarin do not experience this complication, and therefore additional risk factors are likely required to induce necrosis. Protein C and S deficiency, activated protein C resistance, Factor V Leiden, antithrombin III deficiency, or prothrombin gene mutations, and heparin-induced thrombocytopenia may be contributory. Protein C deficiency, either inherited or acquired, is a significant risk factor [89], and has been implicated in more than 50% of cases of WISN. High loading doses of warfarin and inadequate overlap with heparin therapy are also thought to increase risk of early WISN. There are rare reports of cases occurring up to years after the onset of warfarin therapy, and delayed-onset WISN may be related to poor compliance with warfarin, broken up courses of interacting medications, or changing liver synthetic function [89].

WISN generally occurs 3 to 10 days after initiation of therapy. Patients experience pressure or pain in the involved area of skin. Poorly demarcated, indurated erythema develops asymmetrically over fatty areas such as the breast, buttock, thighs, and lower abdomen. Induration progresses over 24 to 72 hours to edema with a *peau d'orange* surface, blue–black discoloration, and hemorrhagic bullae. Localized or widespread full thickness skin necrosis ensues. Histology of involved skin shows noninflammatory thrombosis and fibrin deposition in small dermal vessels with necrosis of the dermis and subcutaneous fat [89].

Differential diagnosis of WISN includes necrotizing fasciitis, APS, DIC or purpura fulminans, calciphylaxis, gangrene, embolic disease, cellulitis, and pyoderma gangrenosum. Recent initiation of warfarin should raise suspicion of WISN.

Screening for hypercoagulable states before anticoagulation is neither predictive of WISN risk nor cost-effective. Low initial loading doses and gradual increases in warfarin levels may decrease risk of WISN. WISN is treated by discontinuation of warfarin, administration of FFP and vitamin K to reverse its effects, and anticoagulation with heparin. Small lesions may be treated conservatively. Extensive involvement may necessitate debridement, grafting, and in extreme cases, amputation. Deep tissue necrosis, secondary infection, and multiorgan failure are more likely with more widespread disease. Even with treatment, the mortality rate is 15% within 3 months of onset. Prior episodes of WISN are not predictive of future occurrences. In most patients with WISN, future warfarin therapy may be reinstituted with caution, avoiding loading doses and overlapping with heparin initially [89].

Cryoglobulinemia

Cryoglobulinemia (CG) is characterized by precipitation of immunoglobulins from serum in cold temperatures. It is classified into three subtypes. Type I CG constitutes 5% to 25% of cases and presents with monoclonal immunoglobulinemia. It is associated with underlying hematologic disease such as multiple myeloma or Waldenstrom's macroglobulinemia. Types II and III CG are the mixed cryoglobulinemias. Type II constitutes 40% to 60% of cases and is associated with a mixture of polyclonal and monoclonal immunoglobulins. It generally occurs in patients with persistent viral infections such as hepatitis C and HIV. Type III CG represents 40% to 50% of cases. It is associated with a polyclonal immunoglobulinemia and with connective tissue disorders.

Two distinct syndromes are seen with CG depending on the subtype. In type I disease, monoclonal cryoglobulins result in hyperviscosity of blood, which may manifest on the skin as livedo reticularis or Raynaud's phenomenon. Cryoglobulins precipitate in cold and result in vascular occlusion or immune

complex-mediated vasculitis which may cause digital ischemia and purpura, respectively.

The mixed cryoglobulinemias are seen in association with infectious and inflammatory diseases. These underlying conditions are thought to trigger B cell hyperactivation, which promotes production of cryoglobulins. Meltzer's triad of palpable purpura, arthralgia, and myalgia may be apparent in 25% to 30% of patients. Other findings include fatigue, neuropathy (70% to 80%), and cutaneous vasculitis. The course in these patients fluctuates. Organ systems other than the skin may be involved as well. The kidneys may be affected in any of the three forms. Bone marrow may be involved in Type I disease, while the peripheral nervous system may be affected in Types II and III.

Diagnosis is based on clinical signs and symptoms and elevated serum cryoglobulin levels. Blood samples should be collected into prewarmed vials and maintained at 37 °C to prevent precipitation of cryoglobulins. While involved skin characteristically shows noninflammatory occlusion of dermal vessels by immunoglobulin precipitates, leukocytoclastic vasculitis may be apparent in up to 50% of cases.

Treatment of mild disease is supportive in nature and otherwise focused on any underlying disease process. For more severe disease, options include immunosuppressive agents, plasmapheresis, rituximab, and radiation or chemotherapy to treat associated hematologic malignancy.

Cryoglobulinemia itself does not typically worsen clinical outcomes of associated disease. Morbidity and mortality are attributed to associated diseases, and death is often due to cardiac disease or infection [90].

Embolic Diseases

Embolization of cholesterol or atheromatous material, fat, or tumor may result in striking systemic and cutaneous findings. Cholesterol embolization is typically a result of interventional vascular procedures such as left heart catheterization or angiograms, and can also be associated with cardiac surgery, thrombolysis, and aortic dissection. Less frequently, patients with severe and extensive atherosclerotic disease may experience spontaneous embolization, or emboli triggered by coughing or straining. Showers of cholesterol and atherosclerotic material travel distally and lodge in small arteries of the CNS, lungs, GI tract, kidneys, and skin. Presenting signs and symptoms of embolic disease include mental status changes, pulmonary edema, heme positive stools, and acute renal failure. Cutaneous findings are striking when apparent and include livedo reticularis, a coarse netlike pattern of violaceous erythema evident on the lower extremities and abdomen (Fig. 195.7). The erythema may be more prominent when the patient is standing compared to the supine position. Tender blue discoloration, petechiae, ecchymoses, ulceration, and gangrene of the feet and toes may eventuate. Pedal pulses are generally intact but bruits may be audible over the femoral artery and abdominal aorta. Calf tenderness is variable. Similar findings on the arm and hands may result from aortic embolization to the upper extremities [91–93].

Fat embolization, seen most commonly after fractures of the long bones or following surgical procedures, is a less common source of embolic disease that presents with the classic triad of pulmonary, neurologic, and cutaneous symptoms. It has rarely been reported following liposuction. Petechiae distributed on the upper body (head, neck, chest, and subconjunctiva) are thought to be pathognomonic and are seen about 50% of the time [94]. Emboli from atrial myxoma, a benign cardiac hamartoma, may result in cyanosis, ecchymoses, splinter hemorrhages, and tender violaceous lesions of the digits [95].

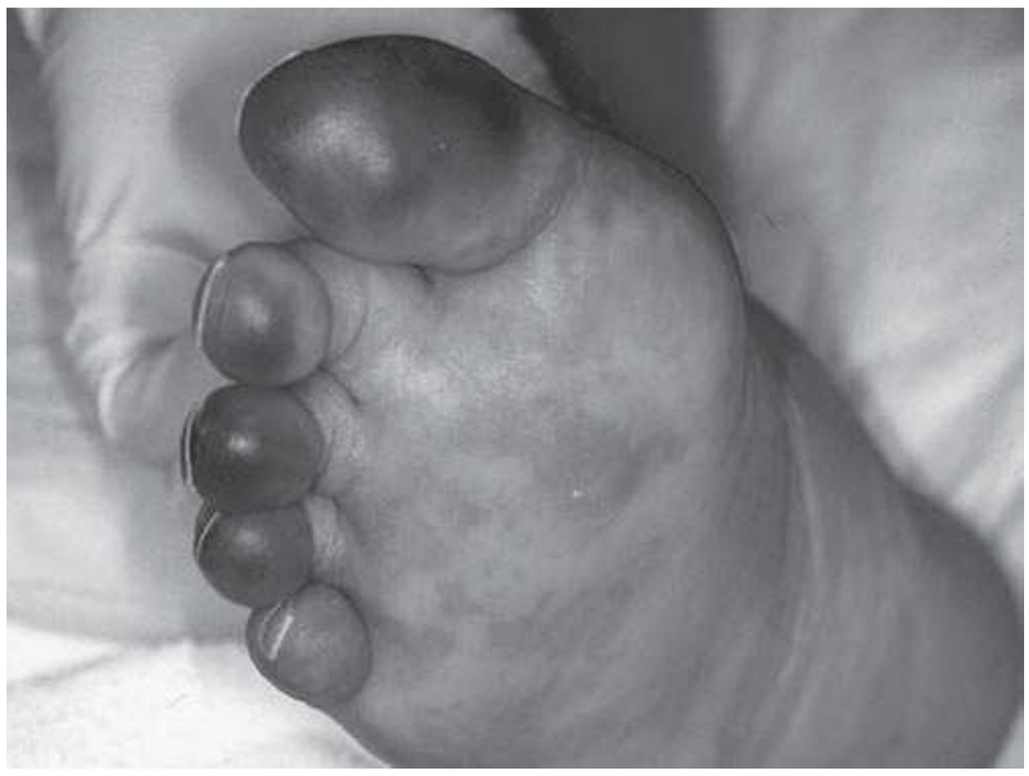

FIGURE 195.7. Cholesterol emboli. Purpuric plaques involving the toes represent areas of necrosis. Note the livedoid (reticulated) pattern on the sole of the foot, an earlier sign of vascular occlusion.

The diagnosis of emboli should be highly suspected in any patient with characteristic skin findings, acute onset end-organ failure, and a recent invasive vascular procedure. Biopsy of the affected organ will show occlusion of vessels with needle-shaped clefts representing cholesterol crystals. Skin is the most accessible and easiest tissue to sample. Atrial myxoma is evident on echocardiogram, and sampling of affected skin will demonstrate the embolized myxomatous material. Laboratory parameters such as BUN, creatinine, CBC and ESR, presence of hematuria, and heme positive stools will be reflective of the organs involved. Treatments include surgical removal or bypass of emboli, amputation of gangrenous digits, and anticoagulation if disease is not thrombolytic-induced [92,95].

Calciphylaxis

Calciphylaxis, or calcific uremic arteriolopathy, is a rare but serious disorder involving calcification of cutaneous arteries and resultant tissue necrosis, usually in the setting of end-stage renal disease (ESRD) and dialysis. Other risk factors include hyperparathyroidism, obesity, white race, female sex, liver disease, malignancy, hypercoagulability, and use of corticosteroids or vitamin D [96]. An elevated calcium phosphate product is not a prerequisite for calciphylaxis, nor is there a correlation between the degree of elevation of calcium, phosphate, or parathyroid hormone levels and the likelihood of developing calciphylaxis. Among patients with ESRD, 1% to 4% develop this disorder.

Calciphylaxis presents with the acute onset of intensely painful indurated purpuric to necrotic skin lesions on a background of livedo reticularis, erythematous papules, plaques, and subcutaneous nodules. Lesions are most common on the thighs, buttocks, and lower abdomen, but may even occur on the digits.

The differential diagnosis of calciphylaxis includes vasculitis, warfarin necrosis, atheroemboli, cryoglobulinemia, APS, protein C or S deficiency, polyarteritis nodosa, and disseminated intravascular coagulation. A deep incisional skin biopsy is usually diagnostic. Calcification is seen in the subcutaneous fat, especially in the medial layer of arterioles, associated with endovascular fibrosis, thrombosis, and necrosis of the subcutaneous fat and overlying skin. Vasculitis is not seen. Laboratory studies addressing causes of hypercoagulability can be helpful as can plain radiographs or technetium 99 bone scans showing vascular calcification.

Treatment of calciphylaxis is controversial and no controlled studies have been performed. Most sources recommend normalization of calcium and phosphorus levels using diet, binding agents, low-calcium dialysis, and sometimes parathyroidectomy [97]. Good wound care and pain control are important. Precipitating factors such as intravenous infusions, oral calcium supplements, or corticosteroids should be avoided or discontinued. Recent studies suggest that use of cinacalcet (30 to 60 mg daily) or sodium thiosulfate (25 gm IV given three times weekly after hemodialysis) may be useful [98]. Overall mortality in calciphylaxis is 80% [97].

CONNECTIVE TISSUE DISORDERS

Systemic Lupus Erythematosus (SLE)

Lupus erythematosus may involve the skin in many forms. Patients with the acute form of cutaneous lupus erythematosus are most likely to have systemic disease, which may be encountered in an ICU setting.

Approximately 80% of patients with SLE have cutaneous manifestations that, although they appear in a multitude of ways, are helpful in identifying affected patients. In fact, 4 of the 11 American Rheumatism Association criteria for diagnosing SLE are cutaneous findings (malar rash, photosensitivity, discoid rash, and oral ulceration). The most characteristic eruption is a transient facial erythema involving the malar area and the bridge of the nose that follows sun exposure (Fig. 195.8). The redness, which may be accompanied by edema, lasts between hours and several weeks before resolving without scarring. This "butterfly" rash may be an indicator of internal disease as it may be associated with anti-dsDNA antibody and lupus nephritis [99].

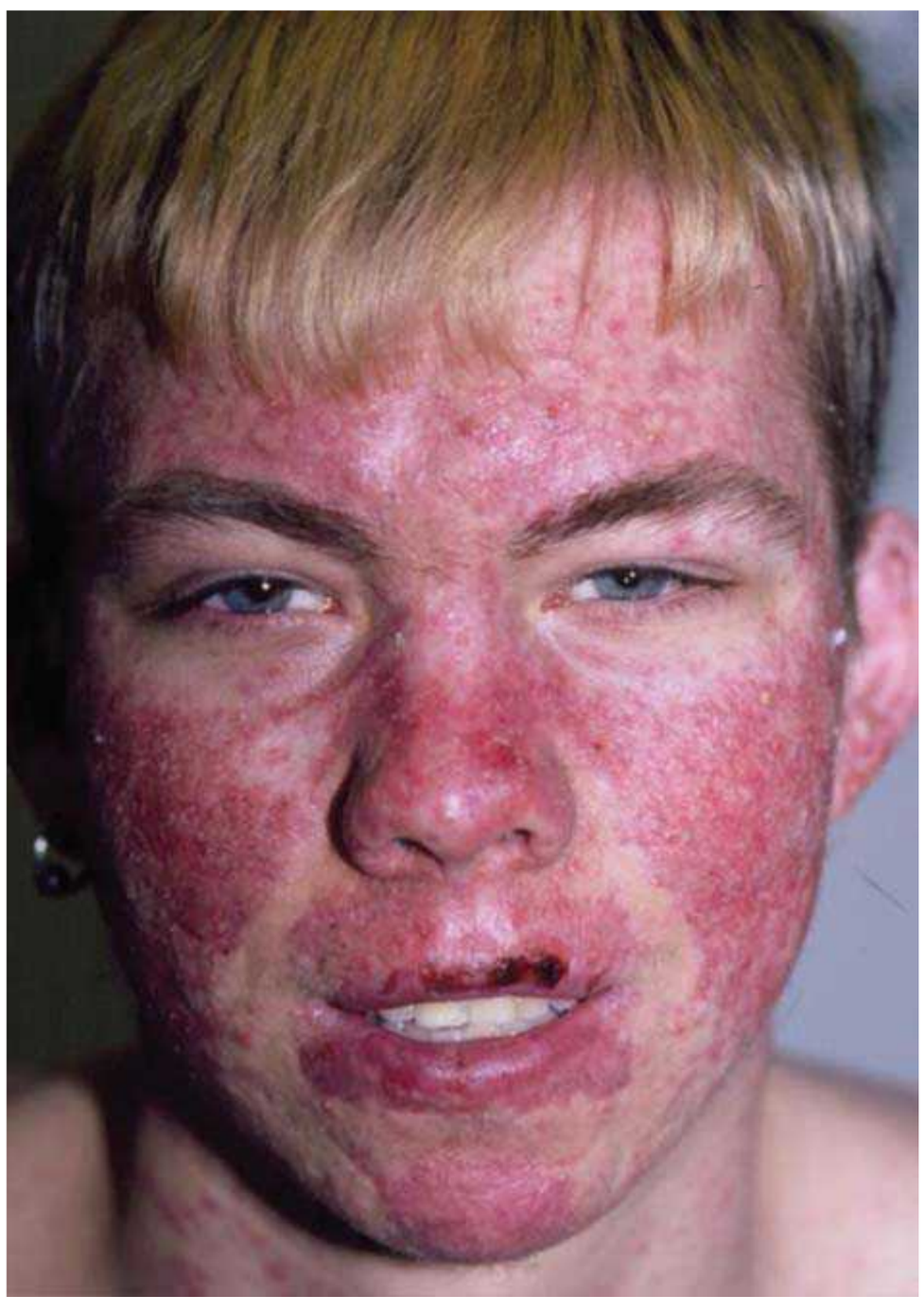

FIGURE 195.8. Cutaneous lupus erythematosus. Marked erythema and telangiectasia involving the malar and other areas of the face.

Erythema and poikiloderma (hyperpigmentation, hypopigmentation, telangiectasia, and atrophy) also occurs over other sun-exposed surfaces such as the V neck area of the chest as well as the back. On the hands, this erythema characteristically spares the knuckles. Tense bullae, also triggered or worsened by sun exposure, may appear in a similar distribution. Mucous membrane lesions occur in about 20% to 30% of patients with SLE. Petechiae or shallow ulcerations may be noted on the hard palate and may accompany malar erythema. Gingival, nasal, and vaginal ulcerations may also be seen.

Scalp hair shedding occurs diffusely and is not associated with scarring. Fragile hairs on the periphery of the scalp break and appear short. Hair shedding may also result from telogen effluvium associated with a chronic illness. Patients with SLE are also more likely to have alopecia areata [99], which typically manifests as oval patches of scalp alopecia.

Vascular lesions, although not specific for SLE, occur in 50% of patients and are highly suggestive of connective tissue disease. The presence of Raynaud's phenomenon, persistent palmar erythema, periungual telangiectasias, purplish plaques over the tips of fingers and toes with cold exposure, and persistent erythema over the palms, soles, elbows, knees, or buttocks should prompt a search for systemic disease.

Vasculitis involving postcapillary venules in the skin manifests as palpable purpura or hemorrhagic wheals. Nodules that ulcerate along the course of arteries reflect deeper, larger vessel involvement. Vascular thrombosis as a consequence of an associated APS causes punched out ulcers that typically appear over malleolar and pretibial surfaces. The presence of livedo reticularis, thrombosis, and cutaneous infarction also warrants consideration of a prothrombotic state.

Less common cutaneous findings in SLE include a symmetric eruption of erythematous papules on the extremities, which demonstrate palisaded granulomatous inflammation with or without vasculitis on light microscopy. Calcinosis cutis, rarely present in SLE, presents as reddish or violaceous firm plaques or nodules on the head, trunk, or extremities.

Other connective tissue diseases should be considered in the differential diagnosis of the acute lupus syndrome. Eruptions of lupus localized to the head and neck may be difficult to differentiate from rosacea, dermatomyositis, drug induced photosensitivity, and sunburn. Drug eruptions or exanthems appear similar when lupus manifests diffusely on the skin.

Treatment of cutaneous lupus is difficult. Strict sun protection along with topical corticosteroids and calcineurin inhibitors are a mainstay of treatment. Antimalarial drugs with or without corticosteroids or steroid-sparing immunosuppressives may be required for systemic or severe skin disease.

Dermatomyositis

Dermatomyositis is a rare disease characterized by a proximal muscle myositis with skin changes. It has a bimodal age distribution and is more common in female and black patients. Initial cutaneous manifestations include swelling of the face and eyelids with a characteristic violaceous erythema. These changes become more widespread with erythema and telangiectasia spreading to the neck and sun-exposed area of the chest, to the back in a shawl distribution, as well as to the scalp, elbows, and knees. These eruptions are usually photosensitive, and pruritus or burning is a common complaint. Gottron's sign, which consists of scaly reddish papules over the knuckle, is considered pathognomonic of dermatomyositis. Hands may take on the appearance of mechanics' hands with hyperpigmentation, scaling, fissuring of the fingertips, ragged cuticles, and enlarged

proximal nail fold capillaries. Intermittent malaise, anorexia, weight loss, and arthralgias are often apparent at this stage. Cutaneous disease usually precedes myositis by months. Juvenile dermatomyositis is relatively rare, and has a better prognosis, but requires aggressive treatment to prevent calcinosis of affected skin. Dermatomyositis may be drug-induced, with hydroxyurea being the most common culprit [100].

Aggressive treatment at this early stage allows for better disease control with lower immunosuppression. Early treatment also reduces the development of disfiguring calcium deposition in the skin and muscle. Initial treatment of skin disease is sunscreen with topical corticosteroids or calcineurin inhibitors, but resistant skin disease may require methotrexate or antimalarials. With evident myositis, therapy requires the use of prednisone (0.5 to 1.5 mg/kg/d tapered slowly over 1 to 2 years) and the addition of a steroid-sparing immunosuppressive such as azathioprine or methotrexate. It is important to also consider the coexistence of other connective tissue diseases such as scleroderma, systemic lupus erythematosus, and rheumatoid arthritis in a patient with dermatomyositis. With appropriate and timely therapy, patients may become disease-free and off therapy within 2 to 4 years. Patients should be surveyed for an occult visceral malignancy which is associated with dermatomyositis in up to 25% of adult cases. Poor prognostic factors include malignancy, older age, initiating therapy after 24 months of muscle weakness, extensive cutaneous lesions, dysphagia, and cardiac or pulmonary issues [101]. A discussion of myositis and systemic disease associated with dermatomyositis is detailed in Chapter 193.

DERMATOLOGIC ISSUES RELATED TO BONE MARROW TRANSPLANTATION

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) occurs in 30% to 80% of hematopoietic cell transplant recipients and is regarded as the primary cause of morbidity and mortality in these patients [102]. Although it is typically a complication of bone marrow and hematopoietic stem cell transplantations, GVHD may also occur in the setting of unirradiated blood product infusion, solid organ transplantation, and maternal–fetal transfusions [103]. Risk factors for GVHD include unrelated donor, HLA mismatch, older age of recipient, female donor with a male recipient, and suboptimal dosing of immunosuppressive drugs. Patients who develop GVHD appear to be at a reduced risk of recurrence of their malignancy, probably due to graft-versus-leukemia or graft-versus-malignancy reactions.

GVHD can occur when immunologically competent donor T cells are transferred to a host that is incapable of rejecting them. The pathogenesis is incompletely understood, but the mediators include donor CD4+ and CD8+ T cells, NK cells, host dendritic cells, macrophages, major and minor histocompatibility antigens on immune and epithelial cells, and cytokines including TNF-α, and IFN-γ [102].

GVHD can be divided into acute and chronic forms, with the acute form developing within the first 100 days after transplantation and the chronic form developing after about day 100.

Acute GVHD

Acute GVHD occurs in 25% to 40% of patients receiving transplants from HLA matched siblings, and it increases to 60% to 80% with 1 HLA mismatch [103]. There is decreased survival from acute GVHD after allogeneic bone marrow transplant. Acute GVHD is classified into four grades based on the extent of skin involvement, serum bilirubin level, and the amount of diarrhea per 24 hours. Skin findings begin with painful or pruritic erythematous macules on the palms, soles, and ears and evolve into a diffuse morbilliform eruption which is often folliculocentric. In severe cases, there may be progression with bullae formation, erythroderma, and skin necrosis. There have been rare reports of acquired ichthyosis as a manifestation of acute GVHD [104]. The differential diagnosis of acute GVHD includes drug eruptions, viral exanthems, and the eruption of lymphocyte recovery. Mucous membrane lesions may be difficult to distinguish from mucositis caused by chemotherapy.

Histopathology of involved skin classically shows an interface dermatitis and apoptotic keratinocytes. However, the utility of a skin biopsy in diagnosing GVHD is controversial. In a small case series, the presence of eosinophils in biopsy specimens was not a reliable marker favoring drug hypersensitivity reaction over GVHD [105]. In three bone marrow transplant recipients with acute skin eruptions, biopsy led to an initial diagnosis of drug eruption, and immunosuppressive therapy was delayed until additional features of GVHD appeared, resulting in considerable morbidity and two deaths.

Chronic GVHD

Chronic GVHD occurs in 30% to 60% of patients and is more common in hematopoietic stem cell transplants compared to bone marrow transplants [102]. A patient's risk of developing chronic GVHD is 11 times higher with a prior history of acute GVHD, but 20% to 30% of patients can develop chronic GVHD without prior acute GVHD [103].

There are two forms of chronic cutaneous GVHD, lichenoid and sclerodermoid. The lichenoid variant is characterized by erythematous and violaceous papules and plaques, often distributed on flexural surfaces that resemble lichen planus. The sclerodermoid form presents with sclerotic, indurated white to yellow plaques that involve the dermis. The process may extend to fascia and result in significant tightening of skin and joint contractures. Lichen sclerosis and eosinophilic fasciitis can also be presentations of the sclerodermoid variant of chronic GVHD [106]. The oral mucosa is often involved and may demonstrate redness and atrophy of mucosal surfaces, lacy white reticulations of buccal mucosa, and ulcerations. Xerostomia is frequently present as well.

COMMON DERMATOLOGIC CONDITIONS COEXISTING IN ICU PATIENTS

Abscess

A cutaneous abscess is a painful, fluctuant, walled-off collection of pus found within the skin. A furuncle represents an abscess associated with a hair follicle and a carbuncle is a collection of multiple furuncles. Abscesses and furuncles are typically caused by *S. aureus*. Patients may carry *S. aureus* in their nares or have Staphylococcal folliculitis as preceding conditions. The clinical presentation consists of a small red papule that evolves into a tender, erythematous deep-seated nodule that may become fluctuant with time. The surrounding area may be warm to the touch if there is an associated cellulitis. The differential diagnosis includes an inflamed epidermal inclusion cyst and an insect bite. Conservative treatment consists of application of warm wet compresses. Incision and drainage may also be performed with culture of contents. As MRSA is becoming increasingly common, lesions that recur or do not

respond to conservative treatment may necessitate appropriate antibiotic treatment based on culture results.

Folliculitis

Folliculitis is a very common disorder characterized by inflammation or irritation of hair follicles. Although cultures are usually negative, Staphylococci, Pseudomonas, or Malassezia furfur are commonly causative. Herpes virus and dermatophytes are less commonly implicated. Folliculitis presents as papules or pustules on an erythematous base with a centrally extruding hair. The lesions may be pruritic and are most often found on the face, scalp, thighs, axillae, and inguinal area. Pseudomonal folliculitis may be more inflammatory and localized to a distribution that would be covered by a bathing suit. Pityrosporum folliculitis may be localized to the upper back and chest and be extremely pruritic. A follicular papulopustular eruption on the face, chest, and upper back has been associated with EGF-R inhibitors and correlates with a positive response to chemotherapy [107]. Diagnostic tools include a potassium hydroxide preparation, Gram stain, and bacterial, fungal, and viral cultures. Treatment is directed at the underlying etiology. Most cases will respond to appropriate topical and/or oral antibiotics (most commonly anti-staphylococcal). Pityrosporum folliculitis requires topical or oral antifungals and Pseudomonal folliculitis may require fluoroquinolones. The prognosis is generally good, but some patients experience recurrent disease [107].

Steroid Acne

Administration of either topical or systemic corticosteroids can lead to the abrupt appearance of an acneiform eruption. In a prospective study of 51 patients receiving intravenous corticosteroids in the setting of acute spinal cord injury, one subject (2%) developed steroid acne [108]. Lesions of steroid acne are usually monomorphic inflammatory papules and pustules that appear on the chest and back. The eruption resolves within weeks of discontinuing the corticosteroids.

Peripheral Edema

Peripheral edema, which is commonly seen in the elderly and hospitalized patients, occurs when capillary hydrostatic pressure and filtration exceeds the lymphatic drainage rate. Common causes of edema include heart failure, renal failure, nephrotic syndrome, cirrhosis, venous thrombosis, or medications, particularly calcium channel blockers. Acute exacerbations of chronic edema may cause edema blisters which present as asymptomatic, noninflammatory tense vesicles and bullae with clear fluid, usually on the distal lower extremities. Edema blisters can be distinguished from other blistering disorders by clinical history and physical examination. If needed, a biopsy for routine histopathology and immunofluorescence may help exclude other blistering disorders. Acute peripheral edema may also produce local dermal edema, leading to induration of the skin and dimpling, known as *peau d'orange*.

Stasis Dermatitis

Stasis dermatitis occurs in the setting of venous hypertension due to valvular incompetence. Risk factors include conditions that exacerbate lower extremity edema such as obesity, congestive heart failure, cirrhotic liver disease, and chronic renal insufficiency. Typically, there is reddish mottling and a yellowish or brown discoloration of the medial lower legs, corresponding to the location of major communicating veins. There may be an eczematous component as well that often results from contact sensitization to topical medicaments applied to the legs. There are often other signs of venous hypertension, including edema, varicose veins, and venous leg ulcers. Over years, the legs may develop lipodermatosclerosis, which occurs when adipose tissue becomes indurated and adherent to fascia, and lower legs take on the appearance of an inverted wine bottle.

The diagnosis is evident in the right clinical context. However, asteatotic eczema, contact dermatitis, and cellulitis may also be considered in the differential. Relief of itching is attained through the regular application of emollients and the use of class IV or V topical steroids. Long-term management involves improving venous return through various measures such as leg elevation above the level of the heart, elastic compression, and exercises to strengthen calf muscles. Care should be taken to avoid trauma to the leg that would facilitate ulcer formation. In severe cases, ligation of incompetent communicating veins may be necessary.

Pressure Ulcers

Pressure ulcers are areas of ischemic soft tissue necrosis resulting from prolonged pressure, shearing force, or friction anywhere on the body. Sites that are most frequently involved include skin overlying bony prominences of the sacrum, ischial tuberosities, heels, greater trochanters, and lateral malleoli. Nonblanching erythema of skin overlying a bony prominence may signify impending ulceration. Other early indicators include warmth, edema, or induration of skin. Initial ulcers appear punched out. Ulceration may occur as partial thickness skin loss, full thickness skin loss involving subcutaneous tissue, or full thickness skin loss extending to muscle, tendon, or bone. Associated pain may be severe and should be managed aggressively. Treatment involves relief of pressure, which may be accomplished through frequent position changes and supportive surfaces such as air, liquid, or foam cushions. Local wound care includes cleansing with normal saline, debridement, and occlusive hydrocolloid dressings to optimize healing. Operative repair is necessary in some cases. Wounds should be monitored for local infection and treated accordingly. Sepsis and osteomyelitis may further complicate ulceration.

Psoriasis

In its most common form (chronic plaque psoriasis), psoriasis presents as chronic well-demarcated erythematous plaques with adherent silvery scale, most commonly over the elbows, knees, and scalp. In guttate psoriasis, there are smaller psoriatic papules and plaques diffusely over the body, and this is often triggered by streptococcal infections. Sudden onset of pustules that coalesce to form "lakes of pus" at the edges of psoriatic plaques associated with fever typifies the more generalized form of pustular psoriasis (Fig. 195.9). Hypocalcemia and pregnancy may be triggering factors in pustular psoriasis. In erythrodermic psoriasis, there is bright red erythema involving $\geq 90\%$ of the skin. These patients are itchy and also complain of chills from the extensive heat loss due to dilatation of cutaneous vessels. In both pustular and erythrodermic forms, patients are generally toxic and may have associated acute respiratory distress syndrome, congestive heart failure, pneumonia, or viral hepatitis (see "Exfoliative Erythroderma" section).

There is a newly recognized association of psoriasis, particularly severe disease, with increased risk of cardiovascular, cerebrovascular, and peripheral vascular disease [109,110].

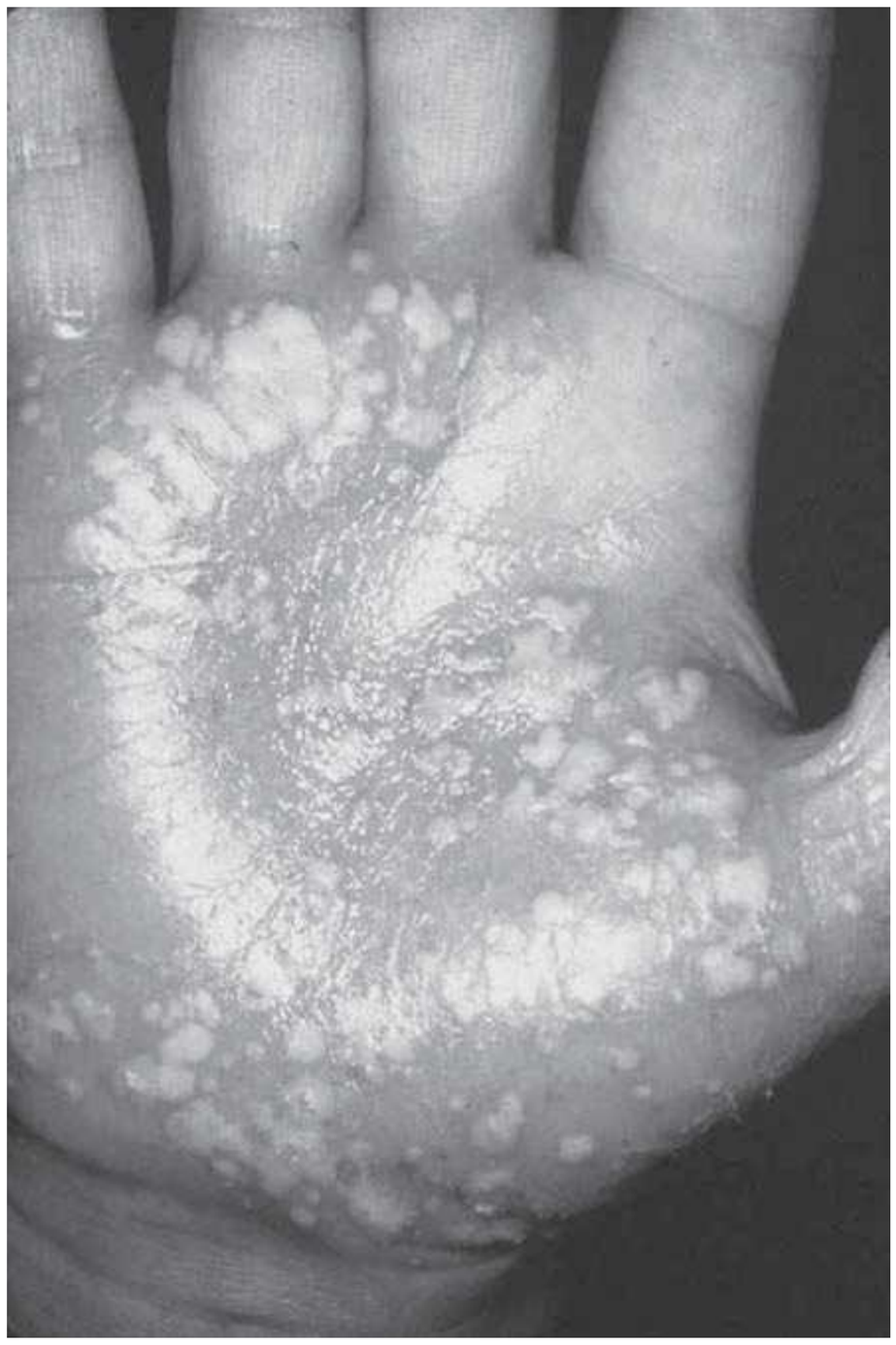

FIGURE 195.9. Pustular psoriasis. Large pustules coalescing to form "lakes of pus" over an area of well-demarcated erythema of the palm.

Treatment of routine cases is with topical corticosteroids and the vitamin D derivative, calcipotriene (Dovonex), whereas more severe cases require ultraviolet phototherapy, methotrexate, systemic retinoids, or TNF-α blocking agents.

Atopic Dermatitis

Atopic dermatitis is characterized by eczematous skin changes and typically involves flexor surfaces in adults, although any body area may be involved. Atopic dermatitis, asthma, and hayfever constitute the atopic triad. The disease is most common in young children in whom the tendency for atopic dermatitis is to gradually improve with age; however, in a minority of patients, disease persists into or manifests in adulthood. In the most severe cases, eczematous dermatitis may evolve into erythroderma (see "Exfoliative Erythroderma" section). Other complications of this disease include secondary bacterial infection (impetigo) or herpetic infection, a condition known as eczema herpeticum. Treatment of atopic dermatitis includes topical corticosteroids, emollients, oral antihistamines, antibiotics as needed, and management of coexisting asthma and allergies.

Contact Dermatitis

Contact dermatitis occurs when direct contact with a substance triggers an inflammatory response in the skin. Irritant contact dermatitis, which accounts for 80% of contact cases, occurs when a chemical directly induces damage to the skin. Common irritants include soap, water, and solvents. The remaining cases represent an immunologically mediated, delayed (Type IV) hypersensitivity reaction. Causes of allergic contact dermatitis in hospitalized patients include adhesives, topical medications, frequently topical antibiotics, preservatives, fragrances, metals, and rubber components.

Acute contact dermatitis, whether irritant or allergic in nature, presents with pruritic papules and weepy vesicles on an erythematous base, initially localized to the area of contact. Chronic lesions are erythematous plaques of thickened skin with accentuated skin markings, scale, and occasionally fissuring. The differential diagnosis may vary depending on the location of the eruption, but generally includes atopic dermatitis, seborrheic dermatitis, stasis dermatitis, and tinea.

History and physical examination are usually sufficient to make the diagnosis. Patch testing may be useful in identifying potentially relevant contact allergens. Treatment involves avoidance of the offending agents. For mild to moderate cases, topical steroids and bland emollients are used. For extensive and severe cases, a 2- to 3-week tapering course of oral prednisone, along with an oral antihistamine to relieve pruritus, is appropriate. For lesions that are oozing and crusting, wet-to-dry or aluminum acetate compresses may be helpful.

Seborrheic Dermatitis

Seborrheic dermatitis is a very common, usually asymptomatic, scaly eruption of the oil-gland bearing skin of the scalp, face, and trunk. It may present in mild cases as common dandruff and in severe cases as a florid erythematous scaling eruption involving the scalp, eyebrows, eyelids, paranasal folds, chest, and axillae. Seborrheic dermatitis typically occurs in perfectly healthy individuals, but is usually most severe in immunocompromised patients, such as those infected with HIV, and in patients with neuropsychiatric disorders. An acute severe presentation should prompt testing for HIV. *Malassezia* yeasts are frequently seen at high levels on the skin of patients with seborrheic dermatitis, but their pathogenic role is unclear. Nonetheless, treatment with antifungals is quite effective.

Diagnosis of seborrheic dermatitis is clinical. The differential diagnosis includes psoriasis, tinea capitis, rosacea, and atopic or contact dermatitis.

Treatment is with antidandruff shampoos containing selenium sulfide, zinc pyrithione or ketoconazole, and topical antifungals (ketoconazole cream, etc.) or mild corticosteroids (hydrocortisone cream). If the patient is not bothered by this rash, it need not be treated.

Transient Acantholytic Dermatosis (Grover's Disease)

Transient acantholytic dermatosis (TAD) is a common eruption consisting of discrete variably pruritic red to brown nonfollicular scaly keratotic papules of the upper trunk seen typically in middle-aged white men, more often in the wintertime. TAD is often seen in bedbound patients and is associated with malignancies. Like miliaria, TAD is often associated with heat and excessive sweating; however, its histopathology, clinical appearance, and treatment are different. Lesions of TAD are more keratotic and scaly than those of miliaria, and histopathology reveals epidermal acantholysis rather than spongiosis. TAD may also be confused with folliculitis, which consists of follicular nonscaly papules and pustules. Treatment of TAD consists of mitigation of heat and sweating, application of midstrength topical corticosteroids (such as triamcinolone cream

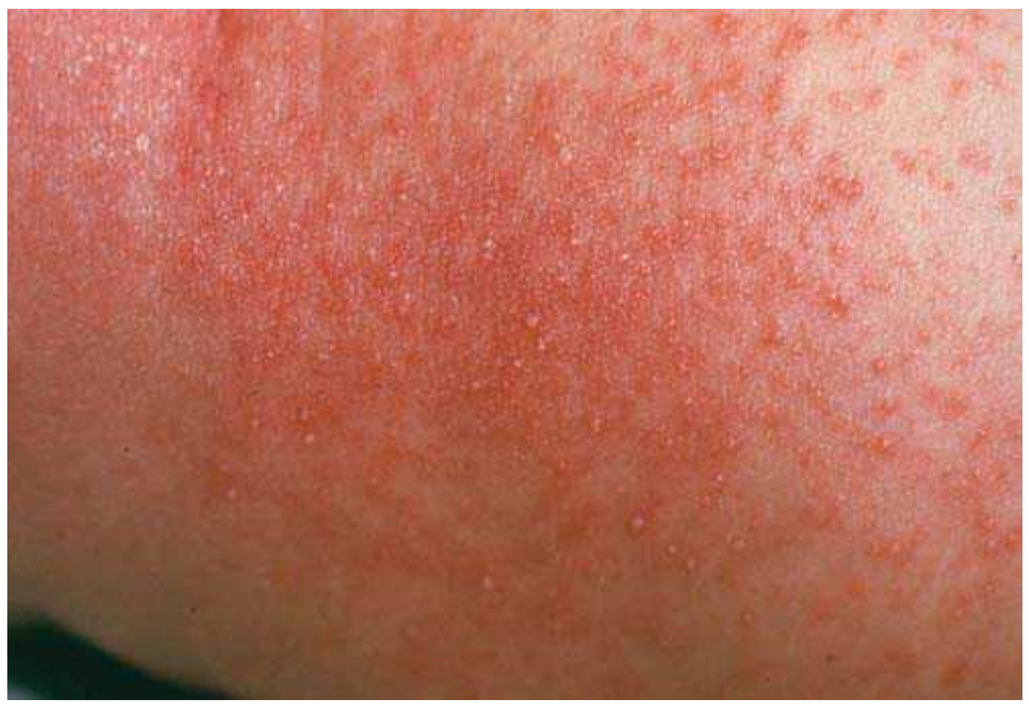

FIGURE 195.10. Miliaria rubra. Tiny nonfollicular inflammatory papules and pustules.

0.1%) twice daily for up to 2 weeks, topical lotions containing pramoxine or menthol, and oral antihistamines (such as hydroxyzine 10 to 25 mg every 6 hours as needed). In severe cases, oral retinoids such as isotretinoin (0.5 to 1 mg per kg daily) may be used. The condition usually remits slowly over weeks to months but can recur.

Miliaria

Miliaria is a common skin eruption in hospitalized patients, caused by blockage of eccrine sweat ducts that occurs with fever and excessive sweating. It occurs in three main forms: miliaria crystallina, which presents as tiny clear asymptomatic superficial vesicles on the trunk, head, and neck; miliaria rubra, which presents as uniform, small pruritic erythematous papules on the trunk, neck, and flexural extremities (Fig. 195.10); and miliaria profunda, which presents as firm, flesh-colored asymptomatic nonfollicular papules or pustules on the trunk and extremities of patients who have had repeated episodes of miliaria rubra. It is important to be able to recognize miliaria to distinguish it from more medically significant entities such as disseminated herpes simplex, varicella, or candidiasis. The distribution of miliaria in areas where the skin is occluded and where excessive sweating occurs is helpful for the diagnosis. Miliaria crystallina does not need to be treated, as it is self-limited and asymptomatic. Miliaria rubra may be treated by decreasing the heat and humidity of the patient's environment. Some reports state that oral ascorbic acid and topical lanolin can be helpful, but no controlled trials have been done [111].

Tinea Corporis

Tinea corporis is a common, superficial fungal infection found on the skin excluding the palms, soles, scalp, and groin. *Trichophyton rubrum* is the most common causative organism, although any dermatophyte may be responsible. Tinea corporis presents as one or multiple annular lesions with erythematous scaly borders that exhibit centrifugal spread and leave a central clearing. Other clinical presentations include Tinea profunda, which exhibits a granulomatous or verrucous appearance due to an excessive host inflammatory response, and Majocchi's granuloma, which presents as follicular-based pustules or papules. The differential diagnosis includes nummular eczema, subacute cutaneous lupus erythematosus, and granuloma annulare. The diagnosis is easily confirmed by potassium hydroxide examination of scale or fungal cultures. Limited disease may be treated with topical agents such as naftifine 1% cream, terbinafine 1% cream, or clotrimazole 1% cream applied twice daily for 2 to 4 weeks. More extensive or recalcitrant disease may require systemic treatment such as itraconazole 100 mg daily or terbinafine 250 mg daily for 2 weeks. Prognosis is excellent with 70% to 100% cure after treatment, but recurrence is common [112].

Scabies

Scabies is a common, extremely pruritic dermatosis caused by infestation with the mite, *Sarcoptes scabiei*. It spreads from person-to-person through direct skin contact, although it can rarely spread through fomites such as bedding or towels. Scabies should be considered in the differential diagnosis of any patient with severe generalized itching, especially if they have had contact with residential institutions such as nursing homes, where it may be epidemic.

Patients with scabies present with severe generalized pruritus, sparing the head and neck, which is worst at night. The pathognomonic lesions are linear burrows (Fig. 195.11), most often found on the hands and feet, especially in the web spaces. Papules, pustules, vesicles, and nodules may also occur, the last being especially common in children. Scabies has a predilection for the hands, feet, wrists, axillae, abdomen, buttocks, and genitalia. Immunocompromised and neurologically impaired patients may present with the crusted or "Norwegian" variant of scabies, in which the skin is markedly thickened and crusted. These crusts are filled with thousands of mites and the patients are highly infectious.

Definitive diagnosis of scabies is made by observing skin scrapings microscopically for mites, eggs, or mite feces. First line treatment of scabies is with topical 5% permethrin cream applied from neck down and left on overnight, with special attention to the genitalia, web spaces, and under the fingernails. All household members or suspected contacts should be treated simultaneously. All bedding, clothing, and towels are then laundered. The application is repeated after 1 week. When topical treatment is impractical, oral ivermectin may be given as a single dose of 200 µg/kg of body weight, repeated in 1 week. Itching usually resolves within 6 weeks of adequate treatment [113].

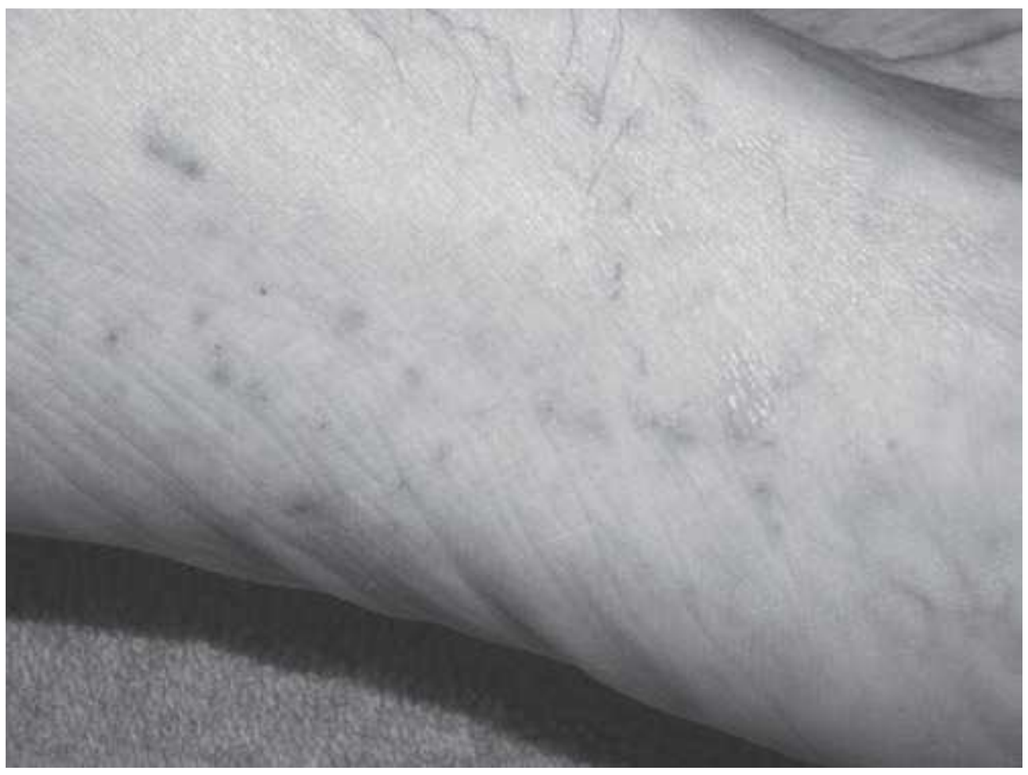

FIGURE 195.11. Scabies. Pink excoriated papules and linear burrows on the foot.

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CHAPTER 196 ■ VASCULITIS IN THE INTENSIVE CARE UNIT

PAUL F. DELLARIPA AND DONOUGH HOWARD

The vasculitides are a group of disorders characterized by the presence of destructive inflammation in vessel walls [1–4]. The possibility of systemic vasculitis should be considered in a patient with systemic complaints and dysfunction of multiple organ systems, frequently in the context of constitutional symptoms such as fever, malaise, and weight loss (Table 196.1). Patients hospitalized in the intensive care unit (ICU) may present with symptoms related to the clinical features associated with a specific vasculitis but may also present with a known diagnosis of vasculitis and complications of treatment, most notably infection.

Vasculitic syndromes typically are classified by the size of vessel involved. Though there may be overlap in the vessel size, diseases may affect predominately large vessels (Takayasu's arteritis), medium-size arteries (such as polyarteritis nodosa and central nervous system [CNS] vasculitis), and small vessels (Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, cryoglobulinemia, and drug-induced vasculitis). These particular vasculitides will be the focus of this chapter. For a more general discussion of vasculitis, other references are noted [1–4].

Disorders not discussed but that may simulate presentation of vasculitis include embolism due to endocarditis, cardiac myxoma, hypercoagulable states including the antiphospholipid antibody syndrome, hyperviscosity syndromes, chronic ergotism, radiation arteriopathy, and, less commonly, Ehlers–Danlos syndrome, neurofibromatosis, Sweet's syndrome, pseudoxanthoma elasticum, and Köhlmeier–Danlos diseases [5,6].

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is a systemic necrotizing arteritis involving predominately medium-size vessels, although sometimes affecting smaller vessels. Vasculitic lesions characteristically occur at the bifurcations or branches of vessels and are often segmental. Almost any organ can be involved, but frequently the skin, peripheral nerves, kidneys, gastrointestinal (GI) tract, and joints are the principal organs affected [7].

Clinical manifestations vary from mild localized disease to multisystem organ failure. Patients generally complain of malaise, weight loss, fevers, abdominal or lower-extremity pain, myalgias, or arthralgias. Clinical parameters include hypertension and azotemia with proteinuria but rarely glomerulonephritis. Peripheral neuropathy occurs in up to 60% of cases, usually involving a mixed sensorimotor and mononeuritis multiplex [8]. Sudden-onset paresthesias associated with motor deficits are common manifestations. CNS involvement, including seizures, focal events, and altered mental status, are less common [9]. Musculoskeletal symptoms including arthralgias (50%), and less frequently, arthritis can occur [7]. Vasculitis of skeletal muscles may cause severe myalgias, and muscle biopsy can be useful diagnostically [10]. Abdominal pain may have a variety of causes, including intestinal angina, mesenteric thrombosis, and localized gallbladder or liver disease. Acute GI bleeding, perforation, and infarction are rare but are associated with a high mortality if the diagnosis is not established promptly [11]. Cardiac involvement, observed in nearly 60% of autopsy series, is often clinically silent and includes congestive heart failure, pericarditis, myocardial infarctions, and conduction abnormalities [12,13]. Cutaneous lesions include nonspecific palpable purpura, livedo reticularis, tender nodular lesions, digital infarcts, and ulcers [14]. Arteritis of the eye, testes, pancreas, ovaries, breasts, and involvement of the temporal arteries may develop rarely.

The pathogenesis of polyarteritis is unknown. Hepatitis B surface antigen has been found in a minority of patients with PAN. The presence of circulating immune complexes of hepatitis B surface antigen and deposition of surface antigen and immunoglobulin in vessel walls has suggested that immune mechanisms may play a role in some forms of polyarteritis [15,16]. Hepatitis C has rarely been associated with PAN [17]. Pathologically, fibrinoid necrosis and pleomorphic cellular infiltration, predominantly with lymphocytes, macrophages, and varying degrees of polymorphonuclear leukocytes involve the entire wall of small and medium muscular arteries. Thromboses and aneurysms can be found in lesions [18].

The diagnosis of PAN focuses on the most frequent areas of involvement, namely, nerve, skin, and GI systems. Laboratory parameters usually include elevated sedimentation rate, elevated C-reactive protein (CRP), and thrombocytosis. Antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), and rheumatoid factor are not typically present in PAN. Mesenteric angiography often shows evidence of aneurysms including the renal, hepatic, and mesenteric arteries, and areas of arterial stenosis alternating with normal or dilated vessels [18]. Sural nerve biopsies are easily accessible sources of nerve tissue when a mononeuritis is present, although the location of biopsy may be guided by electromyography.

Although there is no consensus for treatment of PAN, administration of corticosteroids at 1 mg per kg per day orally is indicated in nearly all cases. In fulminant disease, daily intravenous (IV) methylprednisolone, 1 g per day for 3 days, is reasonable followed by daily oral or intravenous corticosteroids. In the presence of GI involvement, intravenous dosing may need to be continued especially in life-threatening cases. The use of a second drug is guided by the severity of presentation and if there is failure to respond to steroids alone. A severity of illness scoring system (the Five Factor Score) has been developed based on five different parameters, namely, proteinuria more than 1 g per day, azotemia, GI involvement, cardiomyopathy, and CNS involvement. The presence of two or more of these factors portends a mortality of nearly 50% [7]. A review of long-term follow-up of these patients suggests that those with more severe illness as defined with one of the above factors have a higher survival rate when treated with cyclophosphamide [19]. Cyclophosphamide may be given orally, usually 2 mg per kg per day, though adjustment should be made for renal failure (Table 196.2). If the oral route is not feasible, then intravenous dosing of 500 to 1,000 mg per m^2 monthly is

TABLE 196.1

NOTABLE PHYSICAL SIGNS, SYMPTOMS, AND LABORATORY FEATURES OF DIFFERENT VASCULITIC SYNDROMES

Constitutional Symptoms (WG, MPA, CSS, BS, TA, PAN, GCA)	Pulmonary infiltrates/nodules (WG, MPA, CSS)
Sinusitis/epistaxis (WG, MPA, CSS)	Pulmonary hemorrhage (WG, MPA, rarely CSS, BS, Cryo)
Cough, hemoptysis (WG, MPA, CSS, rarely Cryo)	Subglottic stenosis (WG)
Otitis/hearing loss (WG)	Cardiac involvement (CSS, PAN, WG, TA)
Ocular involvement (WG, BS, GCA, TA)	Mononeuritis (WG, PAN, MPA, Cryo)
Cutaneous lesions (WG, PAN, MPA, Cryo, CSS, BS)	Glomerulonephritis (WG, MPA, rarely Cryo)
Claudication (TA, GCA)	Hypertension (PAN, TA)
Arthritis/arthralgia (WG, CSS, MPA, Cryo, PAN)	ANCA positivity (WG, MPA, CSS)
Abdominal pain/GI bleeding (PAN, CSS, BS, MPA)	Angiographic abnormalities (PAN, TA)

ANCA, antineutrophil cytoplasmic antibody; BS, Behcet's syndrome; Cryo, cryoglobulinemia; CSS, Churg-Strauss syndrome; GCA, giant cell arteritis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; TA, Takayasu's arteritis; WG, Wegener's granulomatosis.

appropriate (see Table 196.3). Plasmapheresis (PE) in combination with antiviral therapy is indicated in hepatitis B-associated PAN, though PE does not improve outcome in non–hepatitis B virus PAN [29,30].

A variety of drugs, viral infections, connective tissue diseases such as rheumatoid arthritis, and underlying malignancies may cause a necrotizing angiitis that may be indistinguishable from polyarteritis [31–36].

MICROSCOPIC POLYANGIITIS

Microscopic polyangiitis is a necrotizing vasculitis that involves small vessels, including arterioles, capillaries, and venules. As noted previously, cases of microscopic polyangiitis previously classified as part of the PAN classification were distinguished mainly by the presence of segmental necrotizing glomerulonephritis. Clinical presentations may involve concomitant capillaritis with or without alveolar hemorrhage and rapidly progressive glomerulonephritis, the so-called pulmonary renal syndrome, although more indolent and slower presentations have been described. Glomerulonephritis occurs in nearly all cases, and pulmonary involvement ranging from cough and dyspnea to frank hemoptysis occurs in up to 30% of cases. Neuropathy and cutaneous vasculitis occur in up to 50% of cases [14,35,36].

Pathologically, renal lesions show segmental necrosis, minimal immune or pauci-immune deposition, and crescent formation. In the lung, there is edema of the alveolar wall, neutrophilic invasion, type II epithelial cell hyperplasia, and a paucity of immune deposits. These findings may not be histologically different from those found in patients with Wegener's granulomatosis, and clinically the two entities may be difficult to distinguish. ANCA is found in about 75% of cases, mostly specific for myeloperoxidase (MPO), though occasionally ANCA proteinase 3 (PR3) has been described [36].

Diagnosis is typically made with a biopsy of lung, kidney, skin, or nerve in conjunction with a positive ANCA result. Treatment is similar as described for Wegener's granulomatosis, with corticosteroids at 1 mg per kg per day oral or intravenous methylprednisolone, and cyclophosphamide orally or intravenously [36]. Recent studies comparing rituximab with cyclophosphamide therapy for initial remission induction suggest similar efficacy and toxicities, while rituximab maybe more effective for relapsing disease [27,28]. PE may have a role in the treatment of severe renal disease with evidence suggesting a lower reduced frequency of dialysis, but no mortality benefit [21]. There are no prospective data available regarding the efficacy of PE in diffuse alveolar hemorrhage (DAH), although retrospective data suggest a benefit [37]. In the face of DAH and severe respiratory failure in the setting of a systemic vasculitis, PE in addition to corticosteroids and cyclophosphamide is reasonable as long as every effort has been made to exclude infection. In relapsing disease, intravenous immunoglobulin may be of benefit [20].

TABLE 196.2

DOSAGE ADJUSTMENTS OF ORAL CYCLOPHOSPHAMIDE WITH RENAL IMPAIRMENT

Creatinine clearance (mL/min)	Oral cyclophosphamide dose (mg/kg/d)
> 100	2.0
50–99	1.5
25–49	1.2
15–24	1.0
< 15 or on dialysis	0.8

From WGET Research Group: Design of the Wegener's Granulomatosis Etanercept Trial (WGET). *Control Clin Trials* 23(4):450–468, 2002, with permission.

CHURG-STRAUSS SYNDROME

Churg-Strauss syndrome (CSS) is characterized by the presence of eosinophilic infiltrates and granulomas in the respiratory tract and necrotizing vasculitis in the setting of asthma and peripheral eosinophilia. Typically, patients have a preceding history of asthma and allergic rhinitis and then develop constitutional symptoms of fatigue and weight loss followed by systemic symptoms such as mononeuritis, cardiomyopathy, pulmonary infiltrates, or abdominal pain [14]. Pulmonary disease includes fleeting or diffuse infiltrates and nodular lesions,

TABLE 196.3

RANDOMIZED TRIALS IN THE TREATMENT OF VASCULITIS

Study	Types of vasculitis	Study design	Results	Comment
Gayraud et al. [19]	PAN, MPA, CSS	Meta-analysis of randomized trials	Survival benefits of CYC in addition to CS with FFS ≥ 2	Meta-analysis of four different prospective trials; mixed patient population
Jayne et al. [20]	WG, MPA	Prospective double-blinded placebo controlled, using IVIG in patients with persistent disease activity	Reduced disease activity in IVIG treated group	Short-term follow-up (3 mo)
Gaskin and Jayne [21]	WG, MPA all with renal failure	Randomized controlled trial using either plasmapheresis or pulse CS in addition to standard CS/CYC	Lower rate of dialysis dependence in plasmapheresis treated group	1 year follow-up data only
De Groot et al. [22]	WG, MPA	Prospective, randomized, unblinded comparing MTX to CYC in both induction and maintenance of remission in nonrenal AAV	No difference in the number of patients achieving remission, but higher rates of relapse noted in the MTX treated group	MTX may still maintain remission if initial induction is with CYC
Jayne et al. [23]	WG, MPA	Prospective, randomized, unblinded comparing CYC and AZA in remission maintenance	Relapse rate was not significantly different between the two groups; no difference in AEs	Supports standard of care of changing to AZA once remission induced with CYC
WGET [24]	WG	Prospective, randomized, double-blinded, placebo-controlled trial looking at maintenance of remission with the addition of etanercept or placebo to standard treatment	No increase in remission–maintenance noted in the etanercept group; possible increased malignancy rate in the etanercept group	Shows no role for TNF inhibitors in the maintenance of remission
deGroot K et al. [25]	ANCA associated vasculitis	Prospective randomized controlled trial using oral or IV CYC for induction of remission	No difference in time to remission or proportion of patients who achieved remission	Total dose of CYC less in IV group. Study not powered to detect differences in relapse rates amongst the two groups.
Pagnoux C et al. [26]	WG, MP	Prospective, open label, multicenter trial using either methotrexate or azathioprine as maintenance therapy after remission achieved with CYC and CS.	Relapse rates similar in both groups and AE were similar in both groups.	
Jones RB, et al. [27]	WG, MP: nephritis only	Prospective, open label, multicenter, parallel trial comparing RTX to standard intravenous CYC for induction therapy	Sustained remission rates were similar in both groups and adverse events in both groups were similar	12 month follow-up; small number (44 pts) Patients in RTX group also received IV CYC 15 mg/kg with first and third infusions
Stone, et al. [28]	WG, MP	Randomized, double-blinded, double-dummy multicenter trial comparing RTX to oral CYC for induction therapy	RTX is equivalent to oral CTX in remission induction; no difference in adverse events; RTX may be superior to CYC in relapsing disease	6 months follow-up only and data on maintenance of remission with AZA not available yet 197 patients total

AAV, ANCA-associated vasculitis; AEs, adverse events; AZA, azathioprine; CS, corticosteroid; CSS, Churg-Strauss syndrome; CYC, cyclophosphamide; IVIG, intravenous immunoglobulin; MPA, microscopic polyangiitis; MTX, methotrexate; PAN, polyarteritis; RTX, rituximab; TNF, tumor necrosis factor; WG, Wegener's granulomatosis; WGET, Wegener's granulomatosis etanercept trial.

and peripheral infiltrates occur in up to 75% of patients [38]. The diagnosis of eosinophilic pneumonia may be suggested in the context of peripheral infiltrates and peripheral eosinophilia. Rarely alveolar hemorrhage may occur. Peripheral neuropathy occurs in up to 75% of patients with CSS, whereas renal involvement is much less common than in microscopic polyangiitis and Wegener's granulomatosis. Other sources of morbidity and mortality include GI involvement with bleeding and bowel perforation, cardiac involvement causing arrhythmias, myocarditis, pericarditis, and congestive heart failure [38,39]. The etiology of CSS is unknown. ANCA is positive in approximately 38% to 60% of cases, mostly myeloperoxidase [40–42]. As mentioned earlier, the presence of more than one of the five prognostic factors (i.e., proteinuria ≥ 1 g, azotemia, GI involvement, cardiomyopathy, and CNS involvement) has been associated with a higher mortality and should guide the choice of treatment, suggesting corticosteroids as mentioned above for limited disease and addition of cyclophosphamide in the setting of severe disease [19].

CRYOGLOBULINEMIC VASCULITIS

Cryoglobulins are immunoglobulins that precipitate below 37°C. There are three types: Type I, seen in myeloproliferative disorders; type II, or mixed essential cryoglobulins; and type III, mixed polyclonal. Types II and III are most closely associated with hepatitis C infection. Typical involvement includes cutaneous vasculitis, arthritis, and peripheral neuropathy. Abnormal liver enzymes suggest hepatitis C infection; complement levels, especially C4, are decreased [43,44]. Infrequently, cryoglobulinemic vasculitis may be life threatening with severe renal, GI, and pulmonary involvement including alveolar hemorrhage [45,46]. Therapy in severe cases consists of corticosteroids and cyclophosphamide with careful attention to the potential risk of increased hepatitis C replication. In severe cases involving progressive glomerulonephritis, PE or cryofiltration may be of additional benefit [47–49]. The use of rituximab combined with pegylated interferon and ribavirin may be useful in refractory cases [50].

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is a disease of unknown etiology characterized by granulomatous vasculitis of the upper and lower respiratory tract, segmental necrotizing glomerulonephritis, and systemic vasculitis of small blood vessels [51]. A subset of patients may have disease isolated to the upper respiratory tract or have less severe organ involvement and are referred to as having "limited" Wegener's granulomatosis. Although the disease may affect individuals of a wide range of ages, the disease most commonly affects persons in their fourth or fifth decades of life with a slight predominance for men over women [52,53]. Patients most frequently require intensive care treatment for severe pneumonitis, glomerulonephritis, stroke, myocardial infarction, multiorgan system dysfunction secondary to necrotizing vasculitis, and infection due to immunosuppression and anatomic abnormalities secondary to the granulomatous inflammation.

The etiology of Wegener's granulomatosis is unknown. Possible infectious etiologic associations with *Staphylococcus aureus* have been proposed but are as yet unproven [54]. ANCA is present in more than 90% of patients with systemic Wegener's granulomatosis, and in 70% to 80% with active limited disease. In Wegener's granulomatosis, the pattern noted on immunofluorescence is C-ANCA or cytoplasmic staining, and the specific antigen in most cases is the PR3 antigen, although in 10% of cases or more, there may be a P-ANCA or perinuclear staining with MPO (myeloperoxidase) as the specific antigen [55]. Correlation of ANCA titers with clinical remission is controversial, with the most recent data suggesting that relapse is unlikely in treated patients with negative titers, whereas those with rising or recurrently positive titers have a higher risk of relapse, although the timing of relapse is not predictable [56,57]. There is also increasing evidence of the pathogenicity of ANCA in the vasculitic component of Wegener's granulomatosis [58].

Pathologically, the vessels involved in Wegener's granulomatosis include small arteries and veins; these vessels are often adjacent to granuloma. The pathology of vasculitis includes fibrinoid necrosis with inflammatory mononuclear cell infiltrates of vessel walls, focal destruction of the elastic lamina, and narrowing or obliteration of vessel lumens. Granulomatous lesions are characterized by areas of central necrosis surrounded by epithelial fibroblasts and scattered multinucleated giant cells [59]. Granulomatous vasculitis may involve the lung, skin, CNS, peripheral nerves, heart, and other organs.

Most patients (approximately 85% to 90%) present with symptoms referable to the upper respiratory tract, including sinusitis, nasal obstruction, rhinitis, otitis, hearing loss, ear pain, gingival inflammation, epistaxis, sore throat, laryngitis, and nasal septal deformity. Fever, in addition to being caused by the underlying disease, may be due to suppurative otitis or *S. aureus* sinusitis [60]. Granulomatous vasculitis of the upper respiratory tract may lead to damage of nasal cartilage, resulting in the "saddle-nose" deformity, sore throat, and oral and nasal mucosal ulcers [61]. In addition, chondritis of the nose or ear may develop [62]. Laryngeal involvement may result in severe narrowing of the upper respiratory tract [63,64]. Approximately 10% of patients present with only nonspecific constitutional symptoms such as arthralgias, myalgias, fever, and weight loss. Unusual manifestations of Wegener's granulomatosis include distinctive punched-out ulcerative skin lesions appearing as pyoderma gangrenosum [65] and painless subcutaneous nodules occurring in approximately 2% to 5%.

Although only one third of patients present with symptomatic lung involvement (including cough, sputum production, dyspnea, chest pain, hemoptysis, and even life-threatening pulmonary hemorrhage), lower respiratory tract disease is found in almost all patients after evaluation. The characteristic chest radiographic findings are multiple, nodular, bilateral cavitary infiltrates, but infiltrates without sharp margins occur more frequently than distinct nodules. Cavitation may occur in distinct nodules and in infiltrates with less-defined borders. Nodules may have thick or thin walls. Infiltrates may involve the lower or upper lobes. In approximately 50% of patients, the infiltrates are bilateral. Infiltrates may be transient [64,66]. Less common chest radiographic abnormalities include paratracheal masses, large cavitary lesions, a miliary pattern, massive pleural effusion, calcified nodule, and masses between the trachea and esophagus [67]. Computed tomography (CT) of the chest may reveal pulmonary lesions not well demonstrated on plain radiographs.

Wegener's granulomatosis may also be associated with inflammation and subsequent scarring/stenosis of the subglottic region, in about 25% of patients [68]. This complication is distinctly more common in younger adult and pediatric populations and may sometimes be difficult to differentiate from relapsing polychondritis where tracheal and subglottic inflammation is the major presenting feature.

Although renal manifestations are often asymptomatic, urinalysis reveals renal involvement in approximately 80% of patients at presentation. The typical renal lesion is segmental necrotizing glomerulonephritis. Functional renal impairment may progress rapidly if appropriate therapy is not instituted promptly [69,70].

The vasculitis of Wegener's granulomatosis may cause a variety of other clinical manifestations, including arthralgias and less commonly arthritis, most frequently affecting the knees [71,72]; perinephric hematoma; renal artery aneurysms;

ureteral obstruction [73]; a variety of cutaneous lesions, including ulcers, papules, vesicles, and subcutaneous nodules [66]; episcleritis; conjunctivitis; scleritis; uveitis; optic nerve vasculitis [74]; mononeuritis multiplex or polyneuritis; cranial nerve dysfunction; meningitis [75]; cerebral infarction [76]; subarachnoid hemorrhage; abdominal pain; intestinal perforation; and diarrhea [77].

Typically, diagnosis is based on the clinical findings of upper and lower respiratory tract noninfectious inflammation [78] with glomerulonephritis and positive anti-PR3 antibodies and rarely MPO antibodies. In cases with more limited involvement or where ANCA titers are negative or show the less typical MPO specificity, tissue diagnosis may be necessary.

Recent advances in the treatment of Wegener's granulomatosis have led to the development of a biphasic approach with an initial remission–induction phase using a combination of cyclophosphamide and corticosteroids for 3 to 6 months followed by a remission–maintenance phase using a less toxic immunosuppressive agent, usually methotrexate or azathioprine, for a further 12 to 24 months [79].

Initial treatment with corticosteroid is generally given as prednisone 1 mg per kg per day orally. In the critically ill ICU patient with severe systemic involvement, pulse corticosteroid with IV methylprednisolone 1 g per day for 3 days is advocated, transitioning to prednisone 1 mg per kg per day orally or its IV equivalent. Prednisone therapy is maintained at 60 mg for 1 month and then weaned to 20 mg over 2 to 3 months and then to zero over 6 months.

Cyclophosphamide can be administered as monthly intravenous boluses or as a daily oral dose. Both approaches have shown similar rates of remission–induction at 6 months, 78% with daily oral treatment versus 89% with monthly IV boluses [25]. However, relapse rates were much higher in the monthly IV group, 52% compared with 18% in the daily oral group. In the clinically ill patient, initial treatment with an IV bolus of cyclophosphamide 500 to 1,000 mg per m^2 body surface area is recommended followed by transitioning to daily oral cyclophosphamide 2 mg per kg 4 weeks later. Oral or intravenous doses need to be adjusted for renal impairment. Table 196.2 outlines renal adjustments in oral cyclophosphamide doses. Table 196.3 outlines a standard protocol for the use of IV cyclophosphamide.

Cyclophosphamide therapy is associated with significant morbidity and with patients or their proxy needs to be counseled prior to consent for treatment. There is overall a 2.4-fold increase in malignancy with 11-fold increase in the risk of leukemia or lymphoma and a significant increased risk of bladder cancer occurring in 1% to 3% of Wegener's granulomatosis patients treated with cyclophosphamide [80]. Hemorrhage cystitis has been reported in 12% to 43% of patients treated for Wegener's granulomatosis. In one NIH study, 57% of women of childbearing years became infertile [80]. Opportunistic infection, particularly with *Pneumocystis jiroveci*, was reported in 6% of patients in initial trials with combination cyclophosphamide and corticosteroids and it is now the standard of care for patients to be prophylactically treated with double strength trimethoprim/sulfamethoxazole, 3 times weekly.

Due to these significant morbidities with cyclophosphamide, two recent randomized trials explore the efficacy and safety of rituximab versus cyclophosphamide (one study with intravenous dosing and the second with oral dosing) as induction therapy for ANCA-associated vasculitis. The results in both studies suggest equivalency in inducing remission but also similar adverse event profile [27,28]. Thus, rituximab represents an alternative in induction therapy for patients with ANCA associated vasculitis. The precise role of rituximab in rapidly progressive vasculitis in the critically ill patient is unknown as this was not the focus of the two prospective trials utilizing this agent.

Once remission has been achieved over the first 3 to 6 months, the aim of ongoing therapy is to maintain remission using a less toxic immunosuppressive agent and monitoring the patient closely for signs of relapse. Typical remission–maintenance agents are methotrexate 15 to 25 mg per week orally or subcutaneously or azathioprine 1.5 mg per kg per day orally. Both drugs have been shown to have similar efficacy and side effect profiles in this setting [26]. Mycophenolate mofetil has also shown promise both in remission induction and maintenance [81].

A prospective placebo controlled trial in the use of the tumor necrosis factor inhibitor etanercept as a remission–maintenance agent showed no added efficacy over standard therapy [24]. Treatment of relapsing disease with rituximab may be more effective than repeat cyclophosphamide [28]. Other treatment considerations include management of concomitant upper and lower respiratory tract infections, which are common and difficult to diagnose when superimposed on inflammatory disease.

As mentioned earlier, Wegener's granulomatosis is specifically associated with subglottic stenosis. Optimal treatment of this is best achieved with localized treatment, with bronchoscopic mechanical dilatation, and transbronchial corticosteroid injection of the involved area [82].

DRUG-INDUCED VASCULITIS

Cases of vasculitis associated with the use of certain drugs, vaccines, and toxins have long been recognized. Previously these were described as hypersensitivity reactions causing small vessel vasculitis [83]. More recent work in drug-induced vasculitis has broadened the group to include a large variety of small- and medium-vessel syndromes. There are no specific pathological or clinical features that distinguish this group from other forms of vasculitis. Cases ranging from self-limiting cutaneous involvement to severe multiorgan failure have been reported. Diagnosis is based simply on the development of vasculitis where a causal drug/agent can be identified, which in most cases leads to resolution of the vasculitis after drug discontinuation. There is great variation in the length of drug exposure before symptoms develop, with many reports of years of exposure before the apparent sudden onset of vasculitis.

The most commonly reported medications causing drug-induced vasculitis include, propylthiouracil, allopurinol, hydralazine, cefaclor, minocycline, d-penicillamine, phenytoin, isotretinoin, and methotrexate with colony stimulating factors [84], quinolone antibiotics, and leukotriene inhibitors more recently added to the list [85]. Other cases have been reported following vaccination, particularly hepatitis B [86] and influenza [87].

The pathophysiology of drug-induced vasculitis appears to be varied. Recently, cases of drug-induced vasculitis have been shown to be associated with temporary production of ANCA antibodies, typically against the MPO antigen and most notable with propylthiouracil and allopurinol [88]. Antibody titers also decrease in these cases following the discontinuation of medication, supporting its causal role [89].

Drug-induced vasculitis can involve medium or small vessels and therefore can present with a variety of clinical features depending on the site and size of vessel involved. Drug-induced vasculitis can present with clinical manifestations similar to any other systemic vasculitis, and there are no clinical findings specific to the syndrome. Skin involvement is common, most commonly in the form of palpable purpura. Although 33% of patients have no symptoms associated with the lesions, 40% complain of burning or pain. Bowel and nervous system involvement is also well recognized along with arthralgias and myalgias. Renal involvement is present in 40% of cases.

Treatment involves the withdrawal of potential causative medications. With mild skin involvement alone, no specific treatment is advocated. Where skin breakdown occurs, skin lesions are very symptomatic, or if internal organ involvement is identified, treatment with corticosteroids is beneficial. In rare cases, particularly those associated with ANCA production, other immunosuppressive agents may be necessary but usually only for short periods of time.

CENTRAL NERVOUS SYSTEM VASCULITIS

CNS vasculitis is a rare condition that can present as a primary form confined to the CNS, known as primary angiitis of the CNS (PACNS) or as a secondary form associated with a systemic vasculitis or other systemic illness. Although many of the systemic vasculitides and rheumatologic diseases can result in CNS involvement and are discussed briefly in other sections, this section focuses on the CNS manifestations of PACNS. Other secondary causes of CNS vasculitis and syndromes mimicking CNS vasculitis include sarcoidosis, antiphospholipid antibody syndrome, lymphoma, atrial myxoma, atheroemboli, reversible vasoconstrictive syndrome, Lyme disease, HIV infection, herpes zoster, tuberculosis, and drugs including cocaine, methamphetamines, ergotamine, pseudoephedrine, and heroin [90].

The clinical presentation associated with PACNS is broad and includes subacute memory loss, acute encephalopathy, and other cognitive and behavioral changes. Seizures, cranial nerve abnormalities, focal deficits involving the cerebrum, cerebellum, and brainstem, spinal cord lesions, meningismus, headache, auditory and vestibular disturbances, intracranial or subarachnoid hemorrhage, and reduced visual acuity or blindness due to retinal and optic nerve vasculitis have been described [91,92]. Frequently, patients have hypertension that aggravates their underlying disease or raises questions about their primary diagnosis. Disease manifestations may develop precipitously but often can present with a long prodrome over months involving subtle mental status changes and cognitive dysfunction [91,92]. The disease has a predilection for the small and medium vessels, especially of the leptomeninges and appears more common in men.

The diagnostic approach to CNS vasculitis includes a careful, frequently repeated neurologic examination, laboratory studies including cultures, viral and bacterial serologies, ANCA, cryoglobulins, antinuclear antibodies, antiphospholipid antibodies, and complement levels, which may help to establish secondary causes of CNS vasculitis related to infections, connective tissue disorders, and systemic vasculitides. CSF abnormalities seen in PACNS, including elevated protein levels and elevated cell counts, mostly lymphocytes, occurs in 80% of patients [92]. Angiographic changes showing alternating areas of stenosis and ectasia are suggestive of the disease but can be seen with other diagnoses including vasospasm and infection. In biopsy proven cases of PACNS, angiography is normal in 40% of cases [92,93]. Magnetic resonance imaging (MRI) can additionally be suggestive of ischemic lesions due to vasculitis if lesions are seen in different vascular distributions, although this finding is not specific for PACNS. A negative MRI and normal CSF make CNS vasculitis less likely, although cases of PACNS have been described with a negative MRI [94,95]. In most cases, unless angiography is highly suggestive in the correct clinical context, pathologic confirmation is necessary. Biopsy of the leptomeninges and other areas guided by previous imaging is necessary to rule out other diagnoses including infection, malignancy, and sarcoidosis, among other diagnoses. In PACNS, the inflammatory infiltrate is predominately mononuclear cells, but neutrophils, plasma cells, and histiocytes are also noted [96].

Treatment of PACNS involves corticosteroids (CS) as the initial treatment of choice, ranging from doses of 1 mg per kg per day orally to 1 g intravenously daily for 3 days followed by oral CS. Cyclophosphamide is used in most cases although absolute recommendations are limited by a lack of prospective trials [97].

There are other vasculitic syndromes that can cause similar presentations, as discussed above, although they typically will present with CNS manifestations in the context of other systemic features such as fever, weight loss, peripheral neuropathy, glomerulonephritis, arthritis, or other organ involvement. PAN, Wegener's granulomatosis, and Churg-Strauss syndrome can all present with CNS involvement including seizure, cranial nerve deficit, cerebral vascular events, and subarachnoid hemorrhage [98–101].

OTHER VASCULITIDES

Takayasu's arteritis is a large vessel vasculitis that affects the aortic arch and branches, affecting mainly women up to the age of 50. Patients typically present with constitutional symptoms of fatigue, weight loss, elevated erythrocyte sedimentation rate, and evidence of limb claudication and bruits. Patients can present with stroke due to inflammation and subsequent stenosis of the extracranial vessels [102]. Behcet's disease is characterized by aphthous stomatitis, genital ulcers, and can sometimes present with vasculitis that can affect various-sized blood vessels. Meningoencephalitis, seizure, intracranial hemorrhage, and cerebral vascular events have been reported [103]. Connective tissue disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren syndrome can all be associated with a variety of CNS manifestations including stroke, seizure, encephalopathy, and aseptic meningitis [104–106].

CHOLESTEROL EMBOLISM

Cholesterol crystal embolization can produce a clinical picture very similar to that of a systemic vasculitis [107,108] with the gradual onset of peripheral skin lesions, typically blue toe or livedo reticularis [109], with worsening renal function [110]. Bowel ischemia, acute confusional states [111], and retinal embolization may also be present.

The syndrome occurs due to the release of cholesterol crystals from eroded atherosclerotic plaques. It occurs most frequently following percutaneous endovascular interventions [112,113], but spontaneous episodes or those following anticoagulant [114] or thrombolytic therapy [115] have also been reported.

The chronology of impaired renal function after angiography may help distinguish radiocontrast dye-induced renal failure from renal failure due to atheromatous microemboli. Renal failure caused by radiocontrast dye tends to appear soon after the study, reaches maximal severity within 7 to 10 days, and then improves, with renal function returning to baseline over several weeks. In contrast, renal failure due to atheromatous microemboli to the kidney generally develops over 1 to 4 weeks or even over several months after the angiographic procedure and may not be reversible.

To establish the diagnosis of atheromatous emboli, one must have a high degree of suspicion based on the clinical presentation, history, physical findings, and laboratory results. The diagnosis is confirmed by the demonstration on histologic samples of biopsied skin, muscle, and kidney or amputated tissue of the characteristic biconvex needle-shaped clefts representing the "ghosts" of the cholesterol crystals within arteries and arterioles that are dissolved during routine histologic preparation [116]. With special histologic preparation, the cholesterol

crystals display birefringence when viewed with a polarized light microscope.

Treatment of atheromatous emboli consists of controlling pain and blood pressure, and measures to increase local blood flow with topical glyceryl trinitrate (2% Nitrol) ointment, sympathetic blockade, calcium channel blockers to reduce vasospasm, and perhaps pentoxifylline to improve the rheostatic properties of red blood cells. Newer vasodilator agents such as iloprost and phosphodiesterase inhibitors are also being tried [117,118]. There are also case reports of improvements in cholesterol emboli-associated renal disease with statins [119]. Corticosteroid therapy has also been reported to be helpful in several case reports [120]. There are, however, no controlled trials in the use of any of these agents.

A number of modalities are ineffective for the treatment of atheromatous emboli, including the use of antiplatelet drugs and low-molecular-weight dextran. The use of heparin and warfarin is controversial. The general consensus, however, is that these drugs are contraindicated, because by preventing the formation of an organized thrombus over ulcerated atheromatous plaques, anticoagulants may allow continued breakdown and embolization of material [121]. In cases of chronic distal embolization from abdominal aortic aneurysm, surgical repair or endovascular stent-graft repair usually leads to definitive resolution [122].

TREATMENT STRATEGIES IN UNDIFFERENTIATED RHEUMATIC DISEASES PRESENTING WITH CRITICAL ILLNESS AND RELAPSE OR WORSENING KNOWN RHEUMATIC DISEASE

In certain circumstances, patients present to the hospital or ICU with overwhelming respiratory failure or hemodynamic instability without a previously defined rheumatic disorder. For example, patients with undiagnosed SLE or vasculitis may present with respiratory failure, alveolar hemorrhage, and rapidly progressive renal failure but no specific historical clues or previous serologic data supporting any particular diagnosis, and the results of laboratory and tissue evaluation biopsy may not yet be available. In this situation, one cannot be certain whether the underlying process is an immune complex–mediated disease, such as SLE, Goodpasture's syndrome, or cryoglobulinemia, or a pauci-immune process such as Wegener's granulomatosis or microscopic polyangiitis. The appropriate laboratory evaluation would include an ANCA, ANA, anti-glomerular basement membrane antibody, and cryoglobulins prior to initiating therapy. Initial therapy might include PE, which may transiently remove autoantibodies, cytokines, and complement associated with the inflammatory process, in addition to high-dose methylprednisolone, 1 g intravenously per day for 3 days, and then initiation of intravenous or oral cyclophosphamide [123,124]. The benefit of intravenous immunoglobulin in relapsing or life-threatening vasculitis is not well understood due to a paucity of controlled trials [125,126].

In the face of known rheumatic disease treatment failure, caution must be exercised to exclude infectious sources that may mimic worsening of the underlying disease process. Especially in patients on chronic or high-dose corticosteroids and or cyclophosphamide, particular attention must be paid to exclude opportunistic infections such as *P. jiroveci* and fungal infections such as *Aspergillus* while deciding whether disease activity is escalating and becoming unresponsive to therapy. Once infection has been thoroughly excluded, one can consider either higher doses of a standard or novel immunosuppressive agent or addition of other therapies such as immunoglobulin or PE.

Due to the rarity of systemic vasculitis, there have previously been few prospective clinical trials evaluating accepted treatments. In recent years due to establishment of several investigator consortiums, multicenter prospective studies are now beginning to be performed. The more important of these studies are summarized in Table 196.3.

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SECTION XVII ■ PSYCHIATRIC ISSUES IN INTENSIVE CARE

JOHN QUERQUES

CHAPTER 197 ■ DIAGNOSIS AND TREATMENT OF AGITATION AND DELIRIUM IN THE INTENSIVE CARE UNIT PATIENT

JASON P. CAPLAN

> . . . patients are attacked with insomnolency, so that the disease is not concocted; they become sorrowful, peevish, and delirious; there are flashes of light in their eyes, and noises in their ears; their extremities are cold, their urine unconcocted; the sputa thin, saltish, tinged with an intense color and smell; sweats about the neck, and anxiety; respiration, interrupted in the expulsion of the air, frequent and very large; expression of the eyelids dreadful; dangerous deliquia [syncope]; tossing of the bed-clothes from the breast; the hands trembling, and sometimes the lower lip agitated. These symptoms, appearing at the commencement, are indicative of strong delirium, and patients so affected generally die, or if they escape, it is with a deposit, hemorrhage from the nose, or the expectoration of thick matter, and not otherwise. Neither do I perceive that physicians are skilled in such things as these; how they ought to know such diseases as are connected with debility, and which are further weakened by abstinence from food, and those aggravated by some other irritation; those by pain, and from the acute nature of the disease, and what affections and various forms thereof our constitution and habit engender, although the knowledge or ignorance of such things brings safety or death to the patient.
>
> *Hippocrates, 400 B.C.*

In *On Regimen in Acute Diseases*, Hippocrates identified agitation as a harbinger of severe illness and poor outcome [1]. His admonition that physicians understand the causes and treatments of agitation remains vital today, for the safety not only of patients but also of hospital staff attending to them. Nowhere is this more pertinent than in the intensive care unit (ICU) and its finely balanced environment of invasive and often delicate treatment modalities, interference with which is rarely as easily corrected as is "tossing of the bed-clothes." The sudden pulling of precisely placed central lines, intraaortic balloon pumps, or endotracheal tubes can carry profound consequences for patients and those responsible for their care.

The term "ICU psychosis" has unfortunately entered common medical parlance in reference to agitation and confusion in the ICU patient [2]. This misnomer is inaccurate for several reasons. Classifying agitation as psychosis is usually diagnostically incorrect; moreover, drawing an etiologic connection between the patient's geography and the development of agitation is nonsensical. Historically, sensory deprivation and interruption of normal sleep patterns alone were thought to result in behavioral disturbances in the ICU, but modern research has not confirmed this relationship [2]. The causal attribution of mental status changes to the environment of the ICU is dangerous because it obviates the need for further diagnostic inquiry that could reveal a previously unidentified pathologic process. As with all new symptoms, careful diagnosis is the first step toward effective treatment.

This chapter reviews the causes, presentations, and treatments of common causes of agitation in the ICU patient, focusing on delirium.

DELIRIUM

Perhaps the most common cause of agitation in the general hospital as a whole, and the ICU in particular, delirium is a neuropsychiatric manifestation of a systemic disturbance (Table 197.1) [3]. As such, the paramount task in its treatment is the identification of its underlying cause(s).

Epidemiology

Prospective studies of all patients admitted to the ICU regardless of pathology have found incidence rates of delirium of 31% on admission [4] and 82% when limited to the population requiring intubation and mechanical ventilation [5].

A diagnosis of delirium exacts a profound toll on both the immediate and long-term well-being of patients and the economic resources required for their care. One study of mechanically ventilated patients in the ICU demonstrated significant increases in length of hospital stay and 6-month mortality, even after adjustment for age, severity of illness, comorbidities, coma, and medication exposure [5]. Another study of patients—limited to those who did not require mechanical ventilation—found that a diagnosis of delirium independently predicted longer hospital stay, even after correction for relevant covariates [6]. When framed in fiscal terms, delirium has been associated with 39% higher ICU costs and 31% higher hospital costs overall [7]. Delirium predicts greater hospital costs across multiple domains, including professional, technical, consultative, and nursing [8].

Disruptive behavior poses a grave risk of acute injury to the delirious ICU patient because of the extensive use of invasive technology in the ICU. This hazard has been specifically studied in patients who extubate themselves. Restlessness and agitation—two of the most frequent concomitants of delirium—independently predict self-extubation, which results in laryngeal and vocal cord trauma, emesis, aspiration, cardiac arrhythmia, respiratory arrest, and death [9].

Etiology

An exhaustive review of conditions that may precipitate delirium would likely cover the breadth of medical and surgical practice. Given the near limitless number of possible etiologies,

TABLE 197.1

DIAGNOSTIC CRITERIA FOR DELIRIUM

Alteration of consciousness and attention
Change in cognition (e.g., memory deficit, disorientation, language or perceptual disturbance) that is not due to dementia
Development over hours to days
Fluctuation during the course of the day
Precipitation by a medical condition or its treatment

Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision. Washington, DC, American Psychiatric Association, 2000.

when searching for a possible cause of delirium, it often proves useful to scan the clinical data searching for broad categories of pathology. The mnemonic "I WATCH DEATH" (Table 197.2) lists the processes most commonly related to delirium; the mnemonic "WWHHHHIMPS" (Table 197.3) aids recall of immediately life-threatening causes.

With complicated conditions requiring interventions on multiple fronts, patients in the ICU are often subjected to polypharmacy. A review of the patient's medication list with an eye toward certain categories of medications frequently causative of, or contributory to, delirium is warranted (Table 197.4). Particular offenders include anticholinergics, antihistamines, corticosteroids, opioids, and benzodiazepines [10,11].

Pathology

Alertness is subserved by the ascending reticular activating system (RAS) and its bilateral thalamic projections; attention is mediated by neocortical and limbic inputs to this system [12]. Structural or neurochemical interference with these pathways could theoretically result in the deficits in alertness and attention that are the hallmarks of delirium. Because the primary neurotransmitter of the RAS is acetylcholine, the relative deficit of cholinergic reserve in the elderly (e.g., due to microvascular disease or due to atrophy) may be the neural basis of the heightened risk of delirium in the geriatric population. Medications with anticholinergic activity are likely to disrupt this system's functioning even further.

In the setting of impaired oxidative metabolism, dopaminergic neurons have been found to release excess amounts of dopamine; its subsequent reuptake and extracellular metabolism are also disrupted. Because, at high levels, dopamine is theorized to facilitate the excitatory effects of glutamate [13], this dopaminergic hypothesis constitutes a proposed mechanism for the agitation seen in delirium. In fact, oxidative dysfunction predicts increased risk of delirium [14].

TABLE 197.2

I WATCH DEATH: A MNEMONIC FOR COMMON CAUSES OF DELIRIUM

*I*nfections	Pneumonia, urinary tract infection, encephalitis, meningitis, syphilis
*W*ithdrawal	Alcohol, sedative–hypnotics
*A*cute metabolic	Acidosis, alkalosis, electrolyte disturbances, hepatic or renal failure
*T*rauma	Heat stroke, burns, postoperative state
*C*entral nervous system pathology	Abscess, tumor, hemorrhage, seizure, stroke, vasculitis, normal pressure hydrocephalus
*H*ypoxia	Hypotension, pulmonary embolus, pulmonary or cardiac failure, anemia, carbon monoxide poisoning
*D*eficiencies	Vitamin B_{12}, niacin, thiamine
*E*ndocrinopathies	Hyper- or hypoglycemia, hyper- or hypoadrenalism, hyper- or hypothyroidism, hyper- or hypoparathyroidism
*A*cute vascular	Hypertensive encephalopathy, shock
*T*oxins or drugs	Medications, drugs of abuse, pesticides, solvents
*H*eavy metals	Lead, manganese, mercury

Adapted from Wise MG, Trzepacz PT: Delirium (confusional states), in Rundell JR, Wise MD (eds): *The American Psychiatric Press Textbook of Consultation-Liaison Psychiatry*. Washington, DC, American Psychiatric Press, 1996, pp 258–274.

TABLE 197.3

WWHHHHIMPS: A MNEMONIC FOR LIFE-THREATENING CAUSES OF DELIRIUM

*W*ithdrawal
*W*ernicke's encephalopathy
*H*ypoxia or hypoperfusion of the brain
*H*ypertensive crisis
*H*ypoglycemia
*H*yper- or hypothermia
*I*ntracranial hemorrhage or mass
*M*eningitis or encephalitis
*P*oisons (including medications)
*S*tatus epilepticus

Adapted from Wise MG, Trzepacz PT: Delirium (confusional states), in Rundell JR, Wise MD (eds): *The American Psychiatric Press Textbook of Consultation-Liaison Psychiatry*. Washington, DC, American Psychiatric Press, 1996, pp 258–274.

Risk Factors and Detection

Risk factors for delirium can be divided into three broad categories: properties of the illness (acute physiologic), preexisting properties of the patient (chronic physiologic), and properties of the environment (iatrogenic) (Table 197.5) [15].

The majority of patients suffering from delirium present with the hypoactive subtype. Withdrawn and psychomotorically retarded, the patient with hypoactive delirium is frequently thought by caretakers and family to be depressed. Although these patients cause little disruption to the ICU environment and provoke less acute distress in their treaters, they are no less subject to the adverse outcomes of an altered sensorium. Although the immediate threat to safety may be less apparent in these cases, hypoactive delirium can rapidly and unpredictably evolve into acute agitation as a result of unchecked, upsetting delusions. Moreover, the subjective experience of hypoactive delirium is as intense and distressing as the agitated variety [16].

Two delirium screening scales have been validated for use by nonpsychiatric personnel in the ICU. The Confusion Assessment Method for the ICU (CAM-ICU) features a four-domain assessment that can be administered in less than 1 minute [17]. Both sensitivity and specificity are >90%, and it has been translated into several languages. The Intensive Care Delirium Screening Checklist (ICDSC) features eight items, each scored present or absent. Sensitivity and specificity of the ICDSC are

TABLE 197.4

COMMON ICU DRUGS ASSOCIATED WITH DELIRIUM

- Antiarrhythmics
  - Disopyramide
  - Lidocaine
  - Mexiletine
  - Procainamide
  - Quinidine
  - Tocainide
- Antibiotics
  - Aminoglycosides
  - Amodiaquine
  - Amphotericin
  - Cephalosporins
  - Fluoroquinolones
  - Gentamicin
  - Isoniazid
  - Metronidazole
  - Rifampin
  - Sulfonamides
  - Tetracyclines
  - Ticarcillin
  - Vancomycin
- Anticholinergics
  - Atropine
  - Benztropine
  - Chlorpheniramine
  - Diphenhydramine
  - Eye and nose drops
  - Scopolamine
- Anticonvulsants
  - Phenytoin
  - Sodium valproate
- Antidepressants
- Antiemetics
  - Promethazine
  - Metoclopramide
- Antiviral agents
  - Acyclovir
  - Efavirenz
  - Interferon
  - Ganciclovir
  - Nevirapine
- Baclofen
- Barbiturates
- Benzodiazepines
- Beta-blockers
- Calcium channel blockers
- Digitalis preparations
- Diuretics
  - Acetazolamide
- Dopamine agonists
  - Amantadine
  - Bromocriptine
  - Carbidopa
  - Levodopa
  - Selegiline
- H_2-Blockers
- Immunosuppressants
  - Azacitidine
  - Chlorambucil
  - Cyclosporine
  - Cytosine arabinoside
  - Dacarbazine
  - FK-506
  - 5-Fluorouracil
  - Hexamethylmelamine
  - Ifosfamide
  - Interleukin-2
  - l-Asparaginase
  - Methotrexate
  - Procarbazine
  - Tamoxifen
  - Vinblastine
  - Vincristine
- Ketamine
- Nonsteroidal anti-inflammatory drugs
  - Ibuprofen
  - Indomethacin
  - Naproxen
- Opioids
- Propylthiouracil
- Salicylates
- Steroids
- Sympathomimetics
  - Aminophylline
  - Theophylline
  - Phenylpropanolamine
  - Phenylephrine

Adapted from Cassem NH, Murray GB, Lafayette JM, et al: Delirious patients, in Stern TA, Fricchione GL, Cassem NH, et al (eds): *Massachusetts General Hospital Handbook of General Hospital Psychiatry*. 5th ed. Philadelphia, PA, Mosby, 2004, pp 119–134.

99% and 64%, respectively [18]. The minimal time required to complete either of these scales allows for scoring several times daily, which is an important feature, given the waxing and waning nature of delirium. Both scales are available at www.icudelirium.org. Careful screening and early detection can limit the sequelae of delirium and forestall the additional consequences attendant to the evolution of hypoactive delirium into agitation.

Diagnostic Evaluation

In ambiguous cases of delirium, an electroencephalogram (EEG) may provide objective data to aid diagnosis. Although the association of delirium and EEG changes was first described in the 1940s, no objective test since has demonstrated better performance in accurately detecting delirium. In their classic studies, Engel and Romano described three landmark electrographic findings in delirious patients: generalized slowing, consistency of this slowing despite wide-ranging underlying conditions, and resumption of a normal rhythm with treatment [19]. For all presentations of delirium, generalized slowing in the delta-theta range (delta: 0 to 4 Hz, theta: 4 to 8 Hz), poor organization of the background rhythm, and loss of reactive changes to eye opening and closing are considered diagnostic [20]. Recent studies have estimated the sensitivity of EEG in the diagnosis of delirium to be approximately 75%, with false–negative results likely a result of slowing not sizable enough to drop the patient's baseline rhythm from one range to the next.

EEG may also prove helpful in discerning the etiology of a delirium, since delirium tremens (DTs) as a result of alcohol or sedative–hypnotic withdrawal is associated with low-voltage fast activity superimposed on slow waves, while sedative–hypnotic toxicity is associated with fast beta activity (> 12 Hz) [20]. EEG may also detect previously undiagnosed deliriogenic conditions, including nonconvulsive status epilepticus, complex partial seizures, or cerebral lesions that may act as seizure foci.

Once delirium is confirmed, the search for an underlying medical cause should commence. A careful step-by-step approach can help prune a near-endless list of possible etiologies. Although no evidence-based protocol of diagnostic studies most likely to identify a culprit exists, broad-based, relatively inexpensive, and noninvasive laboratory testing can often be informative (Table 197.6).

In most circumstances, psychiatric consultation is beneficial to the patient and the consultee. A consultation psychiatrist's familiarity with delirium and its causes and treatments usually speeds diagnosis and intervention. Delay in psychiatric consultation predicts lengthier hospitalization [21].

Pharmacologic Management

The definitive treatment of delirium is the identification and treatment of the underlying cause(s). In addition, numerous interventions may reduce its potentially harmful sequelae.

Cholinergic Agents

Given the hypocholinergic/hyperdopaminergic neurophysiological model of delirium, the intuitive goals of pharmacologic treatment are to increase cholinergic and decrease dopaminergic activities. By reversibly inhibiting metabolism of acetylcholine, the cholinesterase inhibitor physostigmine has been shown to reverse delirium resulting from multiple etiologies, but its clinical utility is limited by a brief duration of efficacy and a narrow therapeutic window. Therefore, physostigmine is usually used only when delirium is known (or highly suspected) to be caused by anticholinergic toxicity, for which it is considered the agent of choice [22].

Some small studies and case series of dementia-treating cholinesterase inhibitors have demonstrated possible deliriioprotective effects [23,24], but these agents' utility in the acute setting is hampered by their long half-lives and subsequent extended interval before therapeutic serum levels are reached. Two randomized, double-blind, placebo-controlled trials failed to demonstrate any benefit of donepezil in either preventing or treating postoperative delirium [25,26]. An additional randomized, placebo-controlled trial of rivastigmine for delirium prevention also failed to demonstrate any such benefit [27].

TABLE 197.5

RISK FACTORS FOR DELIRIUM

Properties of illness (acute physiologic)	Properties of patient (chronic physiologic)	Properties of environment/treatment (iatrogenic)
Hyper- or hyponatremia	Age > 70 y	Administration of psychoactive medication
Hyper- or hypoglycemia	Transfer from a nursing home	Tube feeding
Hyper- or hypothyroidism	History of depression	Bladder catheter
Hyper- or hypothermia	History of dementia	Rectal catheter
BUN/creatinine ratio ≥ 18	History of stroke	Central venous catheter
Renal failure (creatinine > 2 mg/dL)	History of seizure	Physical restraints
Liver disease (bilirubin > 20 mg/dL)	Alcohol abuse within 1 mo	
Cardiogenic shock	Drug overdose or illicit use within 1 wk	
Septic shock	History of congestive heart failure	
Hypoxia	Human immunodeficiency virus infection	
	Malnutrition	

Adapted from Ely EW, Siegel MD, Inouye SK: Delirium in the intensive care unit: an under-recognized syndrome of organ dysfunction. *Semin Respir Crit Care Med* 22:115–126, 2001.

TABLE 197.6

ASSESSMENT OF THE PATIENT WITH DELIRIUM

Basic laboratory tests—consider for all patients with delirium	Electrolytes Glucose Albumin Blood urea nitrogen Creatinine Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Albumin Complete blood count Electrocardiogram Chest radiograph Arterial blood gases Urinalysis Thyroid stimulating hormone Vitamin B_{12} Folate Rapid plasma reagin
Additional laboratory tests—consider as clinically indicated	Heavy metal screen Lupus erythematosus preparation Antinuclear antibody Urine porphyrins Urine culture Urine drug screen Ammonia Human immunodeficiency virus antibody Venereal Disease Research Laboratory test Blood culture Serum medication levels (e.g., digoxin, theophylline, cyclosporine, phenobarbital, carbamazepine, FK-506) Lyme titer Cerebrospinal fluid analysis Brain computed tomography or magnetic resonance imaging Electroencephalogram

Adapted from American Psychiatric Association: Practice guideline for the treatment of patients with delirium. *Am J Psychiatry* 156[5, Suppl]: 1–20, 1999.

Haloperidol

As dopamine receptor antagonists, neuroleptics are theoretically suited to the task of dampening dopaminergic activity. Through decades of clinical experience and published data, haloperidol, a butyrophenone neuroleptic, has shown itself to be the agent of choice in the treatment of acute delirium [28,29]. It is ideal for use in the ICU since it can be administered by the oral, intramuscular (IM), or intravenous (IV) route. Although the U.S. Food and Drug Administration (FDA) has not approved the IV administration of haloperidol, FDA regulations permit the use of any approved drug for a non-approved indication or by an unsanctioned route in the context of innovative therapy. IV administration is preferable to the oral and IM routes for multiple reasons, including improved absorption; limitation of pain as a consequence of injection; minimization of apprehension on the part of the patient; and reduction in extrapyramidal side effects (EPS), including acute dystonia, parkinsonism, and akathisia [30]. Although there is no standard dosing regimen for the use of IV haloperidol, treatment is usually initiated with a bolus dose ranging from 0.5 mg (in the elderly) to 10 mg (for severe agitation). A 30-minute interval should be observed between doses to gauge the effect of the previously administered dose. If the initial dose does not achieve the desired effect, then the next dose can be effectively doubled until appropriate sedation is achieved (i.e., 1 mg, 2 mg, 5 mg, 10 mg, and so on). Although a randomized, double-blind comparison trial did not support the use of benzodiazepines alone for the management of delirium (except when due to alcohol or sedative–hypnotic withdrawal), IV lorazepam in doses of 1 or 2 mg can be coadministered with haloperidol to achieve more rapid sedation [31]. The combination of haloperidol and lorazepam has been shown to allow for lower total doses of each drug [32] and to minimize EPS further [33].

Complete absence of agitation should be targeted, and the regimen should be adjusted to achieve this goal. Once agitation is effectively quelled, haloperidol can be given 2 or 3 times daily, with additional doses provided as needed for breakthrough agitation. The total dose can be gradually decreased; it is usually wise to wean the evening dose last to provide some prophylaxis of "sundowning."

Side Effects of Haloperidol. As with all pharmacologic interventions, the use of haloperidol is not without risk. Neurologic sequelae—EPS, seizures, neuroleptic malignant syndrome, and tardive dyskinesia—have all been associated with the chronic

use of haloperidol. In practice, however, these are rare and are minimized by IV administration [30]. Of these neurologic symptoms, akathisia is often most problematic in the setting of delirium since the sense of having to be in motion at all times is noxious, tiring, and likely to exacerbate agitation. Treatment with β-blockade is often effective. In clinical practice, haloperidol's reported lowering of the seizure threshold appears negligible [34].

Hypotension, a rare complication, is easily detected by routine monitoring in the ICU. Haloperidol has been shown in some cases to prolong the QT interval, resulting in increased risk for torsade de pointes and possible death [35,36]. An electrocardiogram should be ordered to measure the baseline corrected QT (QTc) interval, and serum potassium, magnesium, and calcium levels should be checked and monitored [28]. Once treatment begins, a QTc > 500 milliseconds or an increase > 25% from baseline may warrant telemetry, cardiologic consultation, and reduction or discontinuation of haloperidol. In these cases, it is advisable to calculate the QTc manually, since the automated reading may overestimate the value and result in the needless interruption of necessary treatment. The minimization of other drugs with the potential to prolong the QTc should also be considered to allow the ongoing effective treatment of delirium. Other antipsychotics, including the newer agents, have also been associated with QT prolongation [37].

Other Dopamine Receptor Antagonists

Droperidol, the other member of the butyrophenone family of neuroleptics, had been used extensively for the treatment of delirium, but its use was constrained by the 2001 FDA-mandated black-box warning regarding QT prolongation, torsade de pointes, and death [38].

Phenothiazines, the other major class of so-called conventional or first-generation neuroleptic medications (e.g., chlorpromazine, fluphenazine, thioridazine, mesoridazine, perphenazine, and trifluoperazine), are poorly suited to the treatment of delirium due to sedation, anticholinergic effects, and α-adrenergic blockade.

With the exception of clozapine, all of the so-called atypical or second-generation neuroleptic agents (i.e., risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) have been studied in the treatment of delirium [39–42]. Single case reports, case series, retrospective analyses, and open-label studies have found these medications to be safe, well tolerated, and effective.

Quetiapine may have a niche role in the treatment of delirium in patients with Parkinson's disease or Lewy body dementia, since its action at various subtypes of dopamine receptors is less likely to exacerbate these disorders [43]. The strict regulation of clozapine due to the risk of agranulocytosis effectively precludes its use in delirium.

In 2005, the FDA required that a black-box warning be placed on all atypical neuroleptics indicating an increased risk of death when used to treat behavioral problems in elderly patients with dementia and, in 2008, broadened this warning to encompass conventional neuroleptics. In addition, risperidone, olanzapine, and aripiprazole carry warnings regarding a potential increased risk of cerebrovascular events in elderly patients with dementia-related psychosis. The benefits of neuroleptics in treating delirium often outweigh their risks.

Randomized, Controlled Trials of Dopamine Receptor Antagonists in Delirium

To date, there have been five randomized, controlled trials investigating neuroleptics in the management of acute delirium, and two randomized, double-blind, placebo-controlled trials of a neuroleptic for the prophylaxis of delirium (Table 197.7) [31,44–49]. Of the five treatment studies, four demonstrated clinical improvement in delirium with the use of neuroleptics (specifically haloperidol, chlorpromazine, risperidone, olanzapine, and quetiapine). The remaining study by Girard and colleagues used only presence or absence of delirium as a measure

TABLE 197.7

RANDOMIZED, CONTROLLED TRIALS OF NEUROLEPTIC AGENTS IN DELIRIUM

Study	Response examined	Oral agents compared	Total number of patients	Results
Breitbart et al. [31]	Treatment	Haloperidol Chlorpromazine Lorazepam	30	Both neuroleptics significantly improved delirium. No improvement was seen with lorazepam. The lorazepam arm was terminated early due to adverse effects.
Han et al. [44]	Treatment	Haloperidol Risperidone	24	No significant difference was found in efficacy or response rate between haloperidol and risperidone.
Skrobik et al. [45]	Treatment	Haloperidol Olanzapine	73	Clinical improvement was similar for both agents. Haloperidol was associated with extrapyramidal side effects not seen with olanzapine.
Devlin et al. [46]	Treatment	Quetiapine Placebo	36	Scheduled quetiapine resulted in more rapid resolution of delirium, reduced agitation, and improved rates of transfer to home or a rehabilitation facility. Both groups received as-needed intravenous haloperidol.
Girard et al. [47]	Treatment	Haloperidol Ziprasidone Placebo	101	All patients were mechanically ventilated. Neither neuroleptic significantly decreased duration of delirium.
Kalisvaart et al. [48]	Prophylaxis	Haloperidol Placebo	430	Low-dose haloperidol did not reduce the incidence of postoperative delirium. It decreased severity and duration of delirium and length of stay.
Prakanrattana et al. [49]	Prophylaxis	Risperidone Placebo	126	Single-dose risperidone following cardiac surgery significantly reduced the incidence of postoperative delirium.

of clinical status [47]. Since the definitive treatment of delirium requires identification and treatment of the underlying cause, it may not be reasonable to expect that a neuroleptic will completely eradicate all symptoms of a delirium to the point that it is undetectable. Rather, neuroleptics are intended to manage the symptoms of delirium and to reduce the likelihood of further harm to the patient or ICU staff.

Dexmedetomidine

Dexmedetomidine is a selective α_2-adrenergic receptor agonist used as a sedative and analgesic in the ICU. A number of randomized, controlled trials have demonstrated a significantly lower incidence of delirium when ICU patients were sedated with dexmedetomidine compared with midazolam, lorazepam, or propofol [50–52]. An additional study comparing dexmedetomidine with morphine found a comparable incidence but a shorter duration of delirium with dexmedetomidine [53]. A randomized, open-label trial comparing dexmedetomidine infusion with IV haloperidol for the management of delirious intubated patients demonstrated significantly shortened time to extubation and length of ICU stay with dexmedetomidine [54]. Despite the relatively high cost of the drug, two studies have demonstrated it to be cost-effective due to the offset of time spent ventilated, time in the ICU, and the sparing of other expensive sedating agents [52,55].

Prevention

When possible, patient education limits distress from the experience of delirium. If a patient is to undergo a procedure that carries a high risk of delirium, or has multiple risk factors for delirium, preemptively informing the patient of the risk of delirium, describing its clinical course, and emphasizing it may be experientially distressing but that it is not uncommon or permanent have proven helpful in limiting the emotional dysregulation that may lead to behavioral problems later in the course. Similarly, education of the patient's family and reduction of their distress can result in an environment that is more reassuring to the patient and less likely to foment paranoia.

Environmental cues in the ICU can prove invaluable in helping the patient maintain a sense of temporal continuity, thus reducing disorientation. Maintenance of a regular sleep–wake cycle is vital, with lighting cues adjusted to simulate night and day as closely as possible. Noise should be limited at night, although in a busy ICU this may not always be tenable. Televisions should be turned off, and noises from monitors, pumps, and pagers adjusted to a reasonable minimum.

Efforts should be made to orient the patient with a clock, a calendar, and a clearly visible sign indicating the name of the hospital. Measures to increase the familiarity of the milieu with photographs, items from home, and visits from family members can also limit disorientation and distress. Because some patients may be unwilling to report the presence of perceptual disturbances because of fear or shame, frequent reassurance that such phenomena are not a sign of going "crazy" can prevent a frightened patient from acting injudiciously.

One randomized, double-blind, placebo-controlled study examined the use of haloperidol started preoperatively in elderly patients undergoing hip surgery as prophylaxis against postoperative delirium [48]. Results indicated that, while there was no statistically significant decrease in the incidence of delirium, there were significant decreases in severity and duration of delirium and in the length of hospital stay. Another study examined the administration of a single dose of risperidone after cardiac surgery and demonstrated a significant decrease in the incidence of delirium [49].

OTHER CAUSES OF AGITATION

Dementia is a predisposing risk factor for the development of delirium. The demented patient, however, is also at risk of becoming agitated in the ICU as a result of unfamiliar surroundings and possible delusional beliefs. Behavioral measures should be employed to help the patient orient to the milieu. In cases of acute agitation, haloperidol is the treatment of choice; however, in cases of Lewy body dementia, quetiapine is less likely to exacerbate parkinsonian symptoms.

Similarly, the patient with preexisting schizophrenia may have difficulty in understanding and adapting to an ICU stay. Preemptive behavioral measures should be taken to make the ICU as familiar and comfortable as possible.

TABLE 197.8

DIFFERENTIAL DIAGNOSIS OF AGITATION

	Delirium	Dementia	Depression	Schizophrenia
Onset	Acute	Insidious[a]	Variable	Variable
Course	Fluctuating	Progressive[b]	Variable	Variable
Reversibility	Usually	Not usually	Usually	Not usually
Level of consciousness	Impaired	Unimpaired until late stages	Unimpaired	Unimpaired[c]
Attention and memory	Both poor	Poor memory without marked inattention	Attention usually intact, memory intact	Poor attention, memory intact
Hallucinations	Usually visual but can occur in any sensory modality	Visual or auditory	Usually auditory	Usually auditory
Delusions	Fleeting, fragmented, usually persecutory	Paranoid, often fixed	Complex and mood-congruent	Frequent, complex, systematized, and often paranoid

[a]Except when due to strokes, when the onset is acute.
[b]Lewy body dementia often presents with a waxing and waning course imposed on an overall progressive decline. Vascular dementia follows a stepwise pattern, worsening with each successive stroke.
[c]Except when complicated by catatonia.
Adapted from Trzepacz PT, Meagher DJ: Delirium, in Levenson JL (ed): *The American Psychiatric Publishing Textbook of Psychosomatic Medicine.* Washington, DC, American Psychiatric Publishing, 2005, pp 91–130.

Inadequately controlled pain, panic-like anxiety, and a sense of hopelessness resulting from depression can also present with agitation. Anxiety and depression are discussed in Chapters 198 and 199, respectively. Once the trigger for agitation is understood, the appropriate course of treatment is often relatively straightforward. Table 197.8 compares and contrasts several diagnostic traits characteristic of different causes of agitation.

Various substance-withdrawal syndromes may present with agitation and delirium. These often require specific treatment (usually featuring replacement of the dependence-inducing agent and gradual taper) and are covered in Chapter 145.

NONPHARMACOLOGIC TREATMENT OF AGITATION

Despite all efforts to curtail agitated or disruptive behavior, some patients may ultimately require physical intervention to prevent injury to themselves or hospital staff. Interventions range from relatively unobtrusive (e.g., use of mitts to prevent interference with equipment or constant observation to minimize wandering) to more restrictive (e.g., soft limb restraints, Posey vests, four-point locked leather restraints) [28]. Most states and individual institutions have protocols governing the application and documentation of such procedures. Since the application of physical restraints can, in itself, be disquieting to the patient, such intervention should be accompanied by the administration of sedating medication.

LONG-TERM SEQUELAE

Patients diagnosed with delirium are at greater risk for a multitude of neuropsychiatric sequelae long after their discharge from the hospital. Multiple studies have demonstrated increased risk of longstanding cognitive impairment in delirious patients when compared to matched controls [56–58]; one study reported that a diagnosis of delirium resulted in an almost doubled risk of cognitive impairment at 2 years [59]. A review of the available literature by Jackson and colleagues concluded that the presence of delirium (regardless of severity or duration) predicts a greater risk of long-term cognitive impairment, including the development of dementia [60]. Post-traumatic stress disorder (PTSD) has been reported in up to 44% of patients admitted to the ICU [61]. While PTSD may result from the experience of actual physical experiences in the ICU, it has also been reported to occur as the sole result of frightening, hallucinatory, or delusional symptoms experienced in the context of delirium [62]. PTSD is fully discussed in Chapter 198.

CONCLUSION

Agitation in the ICU patient jeopardizes the immediate safety of the patient and may signify a potentially unidentified pathologic process. Delirium is the most frequent cause of agitation and is associated with poorer outcomes across multiple facets of patient care. Careful evaluation of possible causes of delirium is vital, since its only definitive cure is identification and treatment of the responsible underlying condition. Management may involve both pharmacologic and environmental measures, with manipulation of the dopaminergic and cholinergic axes, the primary targets of pharmacologic intervention.

Agitation may also be a symptom of other psychiatric disorders. Preexisting diagnoses of dementia, depression, or psychosis do not rule out the presence of delirium; however, active delirium does rule out the possibility of being able to diagnose a new dementia, depression, or psychosis. Given this level of diagnostic primacy and its manifold associated deleterious sequelae, delirium should be at the cornerstone of any investigation of agitation in the ICU.

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CHAPTER 198 ■ DIAGNOSIS AND TREATMENT OF ANXIETY IN THE INTENSIVE CARE UNIT PATIENT

SHELLEY A. HOLMER AND ROBERT M. TIGHE

Anxiety is a normal, adaptive biological response to threat. It occurs when a person feels helpless and apprehensive about an uncertain future due to a perceived inability to predict or control a desired outcome. In contrast, *pathologic anxiety* is normal anxiety run amok. It occurs spontaneously or amid usually benign circumstances, is excessive in intensity or duration, and impairs functioning and behavior. Anxiety manifests in a variety of ways, resulting in physical, affective, behavioral, and cognitive symptoms and signs (Table 198.1).

Patients admitted to the intensive care unit (ICU) commonly experience anxiety in response to pain, invasive procedures, an unfamiliar setting, and the fear of death. In moderation, anxiety

TABLE 198.1

SYMPTOMS AND SIGNS OF ANXIETY

Physical	Behavioral
Tachycardia	Restlessness
Tachypnea	Agitation
Hypertension	Compulsiveness
Diaphoresis	Avoidance
Light-headedness	Noncompliance with diagnostic or therapeutic interventions
Tremulousness	Fidgetiness
Affective	Cognitive
Uneasiness	Apprehension
Edginess	Worry
Nervousness	Fear of emotional or bodily damage
Fright	Denial
Panic	Obsessiveness
Terror	Preoccupation with harm
	Thoughts about death

can promote healthful behaviors, just as pain can lead to protection from future injury. In excess, however, anxiety can complicate diagnosis, interfere with treatment, and contribute to poor outcomes by increasing both morbidity and mortality. Anxiety can complicate the clinical picture, as symptoms and signs of many medical problems overlap with those of anxiety (e.g., chest pain, palpitations, tachycardia, diaphoresis, tremulousness). Overwrought patients may refuse tests or procedures they fear will cause pain or will lead to bad news. Patients with phobias of blood, needles, and confined spaces (e.g., as in computed tomography and magnetic resonance imaging machines) may forego necessary interventions. Pathologic anxiety may contribute to the need for ICU admission in the first place.

This chapter reviews the physiologic concomitants of anxiety, medical causes of anxiety, critical medical conditions particularly affected by anxiety, anxiety disorders specific to the ICU setting, and the treatment of anxiety.

PHYSIOLOGIC EXPRESSIONS OF ANXIETY

The physiologic expressions of anxiety are myriad. By activating the *fight or flight response*, anxiety recruits the entire autonomic nervous system to respond to an unknown enemy. Multiple organ systems—endocrine, gastrointestinal, musculoskeletal, immune, cardiovascular, and respiratory—are involved [1]. Anxiety increases blood levels of cortisol, prolactin, and growth hormone [2]. A disquieted patient has enhanced gastric motility and gastric secretions, vasoconstriction of the splanchnic and cutaneous circulations, and vasodilation of striated muscle groups [3]. Anxiety also has direct effects on the immune system: a reduction in the chemotaxis of lymphocytes and neutrophils, a decrease in the phagocytic ability of neutrophils, and an increase in plasma levels of tumor necrosis factor α and superoxide anion [4]. This suggests a complex physiologic effect of anxiety in the critically ill population.

The organ systems adversely affected by anxiety of most concern to the intensivist are the cardiovascular and respiratory systems. Anxiety affects the cardiovascular system by altering normal autonomic tone, manifested as increases in heart rate, blood pressure, cardiac output, and cardiac irritability [1]. The stress of simply being hospitalized augments urinary excretion of catecholamines, which represents activation of the sympathetic nervous system and contributes to cardiac arrhythmias [5]. In the fight or flight response, augmentation of cardiac output prevents cardiovascular collapse, but, in heart failure and myocardial infarction (MI), excessive cardiac output can be detrimental. Anxiety increases respiratory rate, tidal volume, and airway resistance [6] and can induce hyperventilation and syncope. These data suggest that anxiety, while exacting a psychological toll, also significantly alters cardiorespiratory physiology, especially in the critical care setting.

MEDICAL CAUSES OF ANXIETY

Because failure to identify and treat *organic* (i.e., *medical* or *secondary*) causes of anxiety can result in increased morbidity and mortality, the distinction between organic and *functional* (i.e., *psychiatric* or *primary*) causes is vitally important. The presence of an organic cause is suggested when anxiety occurs autonomously in the absence of an apparent psychologically charged situation or of a discrete physical event (e.g., acute pain or tachyarrhythmia). However, in any given patient, determination of what constitutes an appropriate or sufficient psychological precipitant for anxiety is difficult. Life history, cultural background, and prior behavioral conditioning are often unknown to clinicians in the fast-paced ICU setting. Therefore, when anxiety is present and no clear psychological or medical cause is obvious, a thorough search for an organic cause is indicated.

Anxiety is a symptom of hundreds of medical conditions; Table 198.2 provides a list of conditions common in the ICU. Two syndromes that are particularly difficult to distinguish from primary anxiety are delirium and substance withdrawal.

Delirium

Treating delirious patients solely with anxiolytics (e.g., benzodiazepines) can exacerbate their confusion, so it is important to distinguish delirium from anxiety by doing a brief cognitive examination. In delirium, performance of tasks of attention, orientation, memory, and language is often impaired; rarely does an anxious patient have these deficits. By definition, delirium always has a medical cause; therefore, determination of its cause, rather than simply treating its symptoms, is vital. Recognition and management of delirium are discussed in Chapter 197.

TABLE 198.2

COMMON MEDICAL CAUSES OF ANXIETY

Neurologic	Respiratory
Delirium	Respiratory failure
Substance withdrawal syndromes	Asthma
Complex partial seizures	Hypoxia
Traumatic brain injury	Hyperventilation
Pain	Pneumothorax
	Pulmonary edema
Cardiac	Pulmonary embolism
Acute myocardial infarction	Toxic
Shock	Illicit drug intoxication
Paroxysmal tachycardia	Anticholinergic intoxication
	Prednisone
Metabolic	Isoniazid
Hypoglycemia	Caffeine
Hyperthyroidism	
Pheochromocytoma	
Cushing's syndrome	
Addison's disease	

Substance Withdrawal Syndromes

Because withdrawal from central nervous system depressants (e.g., opioids, benzodiazepines, alcohol) can be life-threatening, it should always be high on the differential diagnosis of anxiety. This diagnosis can be missed because patients either underreport their substance use or are unable to communicate. Patients can also withdraw from sedatives and opioids prescribed during a lengthy period of mechanical ventilation. Recognition and treatment of withdrawal syndromes are discussed in Chapter 145.

SCENARIOS IN WHICH ANXIETY SIGNIFICANTLY AFFECTS OUTCOMES OF MEDICAL ILLNESS

Acute Myocardial Infarction

As heart disease remains the leading cause of mortality in the United States, *acute coronary syndrome* is a common reason for admission to the coronary care unit (CCU). Prevention and treatment have focused on awareness and alteration of traditional risk factors (e.g., hyperlipidemia, hypertension, family history). A developing literature supports consideration of psychosocial factors as well, most frequently, anxiety, depression, and personality traits [7–11].

Anxiety is a frequent occurrence in the CCU, both related to MI itself and as a premorbid condition contributing to the development of MI [12]. In the general hospital, anxiety has been noted to occur in 24% to 31% of patients after MI [13]. The stress of being cared for in an ICU, particularly the relinquishing of control and privacy, in addition to dealing with a potentially life-threatening disease, contribute to anxiety in this setting [9]. Anxiety in the CCU after MI rapidly rises and peaks within the first 12 hours; declines, though persists, during the next 36 hours; and then increases again as patients face transfer out of the CCU and ultimately discharge from the hospital [14]. Physicians and nurses often under-recognize anxiety and underestimate its severity after MI [15]. Anxiolysis should be an early consideration in post-MI patients.

Physiologically, anxiety-disordered patients have decreased heart rate variability, which may result in an alteration in cardiac autonomic tone [16,17], either by heightened sympathetic stimulation or diminished vagal control [7]. Enhanced sympathetic stimulation is associated with arrhythmias [18], and reduced vagal control is linked with impairment in the baroreflex control of the heart; both perturbations are associated with sudden death [19]. These physiologic changes may explain why anxiety—especially phobic anxiety—enhances risk for sudden death [20,21]. In addition, elevated anxiety is associated with poor implementation of important risk-reducing recommendations after MI, particularly stress reduction, greater socialization, smoking cessation, and adherence to carrying supplies [22].

Two groups demonstrated that anxiety, independent of depressive symptoms, was associated with in-hospital complications after acute MI, including recurrent ischemia, reinfarction, congestive heart failure, and ventricular arrhythmias [9,10]. Further trials are required to determine the nature of this relationship; whether the effect of anxiety is "dose"-dependent; and whether effective anxiety treatment improves cardiac outcomes acutely.

Several studies have looked at the correlation between anxiety and post-MI outcomes in the long term. Some [12,23,24], but not all [25–28], prospective trials demonstrated that high levels of anxiety predicted cardiac events (unstable angina, reinfarction) and/or mortality. Meyer et al. [11] showed that anxiety predicted greater mortality in post-MI patients only if left ventricular function was reduced. These reports suggest that the data for hard cardiac endpoints over the long term remain unclear.

Weaning from Mechanical Ventilation

Respiratory failure and consequent need for mechanical ventilation are common causes of admission to the ICU. Nearly three fourths of patients resume spontaneous, unassisted breathing with little difficulty [29]. However, patients who require prolonged mechanical ventilation have longer hospital stays, face higher morbidity and mortality, and require lengthier rehabilitation. Therefore, the goal is to wean patients as soon as possible.

The experience of shortness of breath has been well associated with anxiety and is one of the most commonly reported symptoms in panic disorder. In fact, anxiety and panic have been shown to lead to hyperventilation, which, when performed voluntarily, induces panic attacks and mediates a wide variety of psychosomatic symptoms [6]. Chronic hyperventilation due to anxiety and panic leads to hypocapnia and slowed recovery from changes in respiratory status. The integral connection between anxiety and respiratory physiology suggests anxiety may contribute to respiratory failure.

Given the limitations of communication and easy fatigability in patients with critical illness, the evaluation of anxiety in this setting remains difficult. Nearly 60% of patients on a ventilator may experience moderate levels of anxiety. The highest levels occur in patients intubated for primary respiratory disorders (e.g., chronic obstructive pulmonary disease [COPD]) and in those on prolonged (> 22 days) artificial ventilation, the very groups who are most at risk for difficulty weaning from mechanical ventilation [30].

Although the physiologic measures used to determine readiness to wean from the ventilator are well known and several of them have been studied closely in clinical trials, information about the effect of the patient's psychological state, specifically anxiety, on weaning from the ventilator is scant. Anxiety may cause shortness of breath and a fear of death or abandonment, especially as ventilatory support is withdrawn. This can stimulate the sympathetic nervous system; cause bronchoconstriction; and increase airway resistance, work of breathing, and oxygen demand. This cascade can become a perpetuating cycle of anxiety, muscle fatigue, and thus weaning failure [31].

Anxiety should be considered in all patients during the weaning process, especially those who are intubated for primary respiratory causes and for a prolonged period. Given the paucity of data regarding the effect of anxiety on ventilator weaning, no clear treatment guidelines exist; however, it is well appreciated that weaning should be approached from a multidisciplinary standpoint. Treatment includes pharmacologic, environmental, and educational approaches, and is enhanced when both patient and nursing staff are involved in the decision to wean and in the process of weaning.

Because anxiety and respiratory distress due to fatiguing respiratory muscles can produce similar cardiorespiratory manifestations, it is important to try to distinguish between these two syndromes. Only if one is convinced that anxiety is the cause should one consider pharmacotherapy for anxiety because pharmacotherapy with benzodiazepines can potentially prolong weaning due to central pump fatigue from respiratory depression (see Chapter 60 on Mechanical Ventilation Part III: Discontinuation). Although this class of medications is associated with respiratory depression and altered level of consciousness, benzodiazepines can be quite effective when used judiciously in the correct setting. Neuroleptics are less associated

with respiratory depression and may be more beneficial than benzodiazepines, especially for patients whose weaning failure is due to fear or to delirious agitation.

More recent evidence suggests a role for dexmedetomidine, an α_2-adrenergic receptor agonist, which causes a rapid onset of sedation and analgesia but not respiratory depression [32–34]. The lack of respiratory-depressant effects allows patients to be extubated while remaining on dexmedetomidine, whereas benzodiazepines require discontinuation or reduction prior to extubation. Though not specifically studied in anxious patients, dexmedetomidine demonstrates adequate sedation and decreased time on the ventilator, suggesting that it may be a useful agent in the anxious patient attempting to wean from the ventilator.

Nursing support is critical in successful weaning. Staffing should remain as consistent as possible with an individual patient, and during active weaning, a 1:1 nurse-to-patient ratio should be maintained. Weaning is more successful when patients are aware of their environment and engaged in discussions of the plan and process of weaning. Patients should be told and reminded that weaning without extubation does not represent a failure but is part of the process. Music therapy has been associated with decreased anxiety levels in ICU patients and may facilitate weaning [35].

Asthma

Up to 8.9% of adults in the United States have been diagnosed with asthma; of those, 3.4% have experienced an episode in the preceding 12 months [34]. In a multicenter study in 2000, 10% of 29,430 admissions for asthma were to the ICU and 2.1% of these patients were intubated [36]. Despite the advent of inhaled corticosteroids in 1972, there continues to be a population of patients with brittle or near-fatal asthma that follows a poor clinical course even with aggressive use of anti-inflammatory agents. This has re-heightened attention to psychological factors (e.g., anxiety, depression, and denial) as a possible focus of intervention in these patients.

Anxiety has a strong association with asthma, particularly in severe cases admitted to the hospital. Anxiety-spectrum disorders have been identified among individuals suffering near-fatal asthma attacks, and patients who deny the disease process are more likely to develop near-fatal asthma attacks [37,38]. A prospective study of children with asthma identified a relationship between stressful life events and new asthma attacks both immediately and 5 to 7 weeks after a stressful event [39]. Despite this, there appears to be no difference in anxiety or other psychological parameters in adults with severe, life-threatening asthma compared to asthma patients requiring hospital admission [40]. Due to the retrospective reporting in many of these studies, however, a causal relationship between anxiety and asthma cannot be confirmed; moreover, whether the association is due to a direct physiologic impact on airway resistance or reflects a comorbid disease process is not known [41]. Despite the lack of answers, it is clear that asthmatic patients suffer from higher rates of anxiety. For this reason, anxiolysis in ICU patients admitted for asthma exacerbations may need to be considered.

ANXIETY DISORDERS SPECIFIC TO THE INTENSIVE CARE UNIT

Patients with a variety of anxiety disorders present to the ICU. Symptoms associated with these conditions can be exacerbated by the acute medical or surgical problem that led to the ICU admission. In addition, medications used to treat a preexisting anxiety disorder may be discontinued on admission, or their bioavailability may be altered by interactions with newly prescribed medications. Both discontinuation and pharmacokinetic changes may significantly worsen preexisting primary anxiety disorders. In addition to exacerbating established psychiatric illnesses, the experience of the ICU can lead to new, longstanding anxiety disorders [42]. Anxiety disorders particularly relevant in the ICU include acute stress disorder (ASD), posttraumatic stress disorder (PTSD), and panic disorder.

Acute and Posttraumatic Stress Disorders

The experience of treatment in the ICU—which includes frightening confusion, painful invasive procedures, and fear of death—can be traumatic for many patients. Often, especially in the surgical ICU, patients are admitted due to a traumatic event (e.g., motor vehicle accident, severe burn, and assault). These circumstances predispose patients to the development of ASD and PTSD.

Diagnosis of both ASD and PTSD requires clinically significant distress following an experience of threatened death or serious injury, which engenders intense fear, helplessness, or horror in the traumatized person. That event is then re-experienced through dreams, intrusive memories, flashbacks, or intense distress when exposed to reminders of the event. Other characteristic symptoms include emotional numbing, anhedonia, amnesia, restricted affect, and symptoms of autonomic arousal (e.g., irritability, hypervigilance, and exaggerated startle response). For a diagnosis of ASD, these symptoms must occur within the first month after the trauma; if symptoms persist beyond 1 month, a diagnosis of PTSD should be considered.

Some patients develop syndromes consistent with both ASD and PTSD consequent to events that occur in the ICU. The prevalence of PTSD in ICU patients has been widely studied. A systematic review of the literature found the median point prevalence of clinically significant PTSD symptoms to be 22% (range 8% to 51%), significantly higher than the 3.5% prevalence of PTSD in the general population [43,44]. The risk of developing ASD and PTSD is presumed to be even higher in patients who are admitted to the ICU after a trauma.

There is a burgeoning literature about the prevention of PTSD related to critical care. Several studies have attempted to identify risk factors for developing ICU-related PTSD; the most robust risks are: preexisting anxiety and depression, greater ICU benzodiazepine administration, and memories of in-ICU frightening experiences, nightmares, and delusions [43]. The positive correlation between benzodiazepines and PTSD symptoms may be due to the need for higher doses of these medications in patients with preexisting psychiatric conditions. However, benzodiazepines are likely an independent risk factor for PTSD because they often result in delirium and prolonged sedation, both of which may spawn frightening agitation and delusions and necessitate physical restraint. When patients with ICU-associated PTSD report the content of their intrusive memories and nightmares, they are commonly false memories laid down during periods of delirium or sedation. These false memories fill in memory gaps such that true memories of the ICU stay become interwoven with fragments of dreams, delusions, and hallucinations [45]. Isoflurane may have an advantage over midazolam for sedation in reducing memories of delusions and hallucinations [46]. Studies indicate that false memories of the ICU stay are correlated with higher rates of PTSD and worse health-related quality of life [47–49]. Therefore, interventions that target delirium, disorientation, and faulty reality testing may prevent the development of PTSD. Though the provision of a self-help rehabilitation manual did not reduce anxiety or PTSD symptoms compared to usual care, patients who read a daily-event log recorded for them during their critical care

TABLE 198.3

SYMPTOMS OF A PANIC ATTACK

Neurologic	Respiratory
Feeling dizzy, unsteady, light-headed, or faint	Dyspnea
Feeling unreal or detached from oneself	Sensation of smothering
Fear of losing control, going crazy, or dying	Feeling of choking
Paresthesias	Gastrointestinal
Cardiovascular	Nausea
Palpitations	Abdominal distress
Pounding heart	Miscellaneous
Tachycardia	Diaphoresis
Chest pain or discomfort	Trembling
	Shaking
	Chills
	Hot flashes

Adapted from reference 65.

admission had less anxiety compared to patients who did not read such a diary [50,51].

Even in the absence of delirium, prolonged sedation may contribute to the development of PTSD. Studies comparing daily sedation withdrawal to continuous sedation and light versus deep sedation showed fewer PTSD symptoms with sedation withdrawal and light sedation [52,53].

Studies of psychopharmacologic intervention for the prevention of PTSD have yielded mixed results. Several studies have demonstrated a decrease in the prevalence of PTSD in critically ill patients treated with stress doses of corticosteroids, which are thought to have an effect on traumatic-memory retrieval [54–57]. There is also evidence that treatment with β-receptor antagonists may protect against the development of PTSD, perhaps by blocking catecholamines, which enhance memory of emotionally arousing experiences [58–61]. However, this benefit was not seen in a randomized, controlled trial of critically ill patients [62]. Further research is necessary before prophylactic treatment with either corticosteroids or β-blockers becomes a standard intervention.

In the ICU, acute trauma should be treated with supportive reassurance and symptom-targeted medications. Clinicians should identify and treat delirium, make efforts to reduce unnecessary sedation, and help orient patients to what is happening around them. A recent study identified other modifiable predictors of PTSD: memories about pain, lack of control, and inability to express needs [63]. These can be addressed with appropriate pain assessment and management, allowing patients more choices in their care, and helping patients to communicate (e.g., using Passy-Muir valves in tracheostomized patients). Psychiatric consultation can be useful for both acute management and recommendations for outpatient treatment, especially in patients with preexisting psychiatric illnesses.

Panic Disorder

Panic disorder is one of the most common psychiatric disorders in patients who are high users of medical services. The risk for development of panic disorder is higher in patients with mitral valve prolapse, asthma, COPD, and migraine [64]. As defined

TABLE 198.4

SOME INTRAVENOUS MEDICATIONS FOR THE TREATMENT OF ANXIETY

Drug	Typical dose	Onset (min)	Drug interactions	Side effects
Lorazepam	0.04 mg/kg	5–15	Fewer drug interactions than other benzodiazepines	Respiratory depression, mixed in propylene glycol solution, venous irritation
Diazepam	0.1–0.2 mg/kg	1–3	Effects increased by cimetidine, erythromycin, isoniazid, ketoconazole, metoprolol, propranolol, valproate Effects decreased by rifampin and theophylline	Respiratory depression, mixed in propylene glycol solution, venous irritation
Midazolam	0.025–0.35 mg/kg	1–3	Same as diazepam	Respiratory depression, accumulates with prolonged (> 48 h) use, excessive sedation
Propofol	0.25–1 mg/kg (loading dose) then 1–6 mg/kg (continuous infusion)	< 1	Minimal	Respiratory depression, vasodilation particularly with bolus dosing and in hemodynamically unstable patients
Haloperidol	1–5 mg	20–30	Effects decreased by rifampin Medications that widen QT interval	QT interval prolongation, neuroleptic malignant syndrome, EPS (less with IV than with oral use)
Dexmedetomidine	Initial recommended dose: 0.8 μg/kg/h titrated to a dose between 0.2 and 1.4 μg/kg/h	6	Minimal but has the potential to augment bradycardia induced by vagal stimuli or negative chronotropic drugs and may increase the effects of vasodilators	Hypotension, bradycardia

EPS, extrapyramidal symptoms; IV, intravenous.
Adapted from Marino PL (ed): *The ICU Book*. 2nd ed. Baltimore, Lippincott Williams & Wilkins, 1998; and Eisendrath SJ, Shim JJ: Management of psychiatric problems in critically ill patients. *Am J Med* 119:22, 2006.

by the *Diagnostic and Statistical Manual of Mental Disorders* [65], a panic attack is a discrete period of fear or discomfort that develops suddenly, reaches a peak within 10 minutes, and is associated with the symptoms listed in Table 198.3. Panic disorder consists of recurrent panic attacks accompanied by persistent fear of having additional attacks, worry about the implications and consequences of the episodes, and a significant change in behavior related to the attacks. Many panic-disordered patients are hypervigilant to internal bodily stimuli, and some fear that their attacks indicate the presence of an undiagnosed, life-threatening illness. These concerns are assuaged only when the panic disorder is accurately diagnosed and effectively treated.

Risks for developing panic attacks include separation, disruption of important relationships, and medical illness—all endemic in the ICU. Timely diagnosis and treatment of panic disorder can circumvent unnecessary medical procedures and decrease morbidity and mortality. Additionally, the physiologic consequences of panic may exacerbate symptoms of preexisting medical conditions and lead to more frequent medical hospitalizations. However, because its presentation is similar to that of several medical conditions (e.g., MI, stroke, gastrointestinal conditions, respiratory compromise), especially in the ICU, panic disorder must be considered a diagnosis of exclusion. Treatment for panic disorder includes psychotherapy and medication. Cognitive-behavioral techniques (e.g., psychoeducation, anxiety management skills, cognitive reframing, and exposure to somatic cues) have been well studied. Benzodiazepines and antidepressants—specifically the selective serotonin reuptake inhibitors (SSRIs)—are the standard of care for the psychopharmacological management of panic disorder.

TREATMENT OF ANXIETY IN THE INTENSIVE CARE UNIT

Treatments for anxiety in the ICU include both nonpharmacologic and pharmacologic options. Additionally, the stress placed on medical and nursing staff attending to anxious patients in an emotionally charged treatment setting must be acknowledged and addressed to improve the overall care of anxious patients in the ICU. This topic is reviewed in Chapter 202.

Nonpharmacologic methods that have been explored include education, environmental manipulation, muscle relaxation, and music therapy. The data supporting these practices are limited and equivocal. Nonetheless, these therapeutic modalities have been useful in clinical practice.

TABLE 198.5

RANDOMIZED TRIALS OF ANXIETY TREATMENTS IN CRITICALLY ILL PATIENTS

Study	Enrollment	Intervention	Results
Sackey et al. [46]	40 mechanically ventilated ICU patients	Isoflurane vs. midazolam	Trend toward fewer memories of delusions/hallucinations in the isoflurane group. No differences between groups in memories of feelings or factual events or in anxiety, depression, and well-being scores.
Jones et al. [50]	126 ICU patients	Self-help rehabilitation manual vs. routine follow-up	Trend toward a lower rate of depression in intervention group. No differences in anxiety and PTSD symptoms between groups.
Knowles et al. [51]	36 ICU patients	Prospective diary reviewed postdischarge vs. standard of care	Improvement in both depression and anxiety symptoms in experimental group.
Kress et al. [52]	32 mechanically ventilated ICU patients	Daily sedation withdrawal vs. continuous sedation	Fewer PTSD symptoms in daily sedation withdrawal group.
Treggiari et al. [53]	137 mechanically ventilated ICU patients	Light vs. deep sedation	Fewer symptoms in the light sedation group at 4 weeks. No differences in anxiety and depression between groups.
Schelling et al. [55]	91 patients undergoing cardiac surgery, 48 followed up in 6 months	High-dose corticosteroids perioperatively vs. standard care	Reduced PTSD symptoms in the steroid group. No difference in traumatic memories between groups.
Weis et al. [56]	36 patients undergoing cardiac surgery	Stress-dose hydrocortisone vs. placebo	Reduced incidence of chronic stress symptoms and better health-related QoL in steroid group. No difference in traumatic memories between groups.
Schelling et al. [57]	20 patients with septic shock	Stress-dose hydrocortisone vs. placebo	Lower incidence of PTSD in intervention group. No difference in traumatic memories between groups.
Stein et al. [62]	48 patients admitted to a surgical trauma center	Propranolol vs. gabapentin vs. placebo	No differences in PTSD symptoms, depression, or ASD at 1, 4, and 8 months after injury.
Ziemann et al. [66]	41 CAD patients admitted to a CCU	Individualized contact with nurse vs. usual care	Significantly less anxiety, depression, and hostility in the experimental group.
Corbett et al. [67]	89 mechanically ventilated patients after nonemergent CABG	Propofol vs. dexmedetomidine	No differences in pain, anxiety, and sleep/rest between groups.

ASD, acute stress disorder; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCU, coronary care unit; ICU, intensive care unit; PTSD, posttraumatic stress disorder; QoL, quality of life.

Patients should be made aware of their clinical situation and oriented to their environment. Provision of ambient light, a clock, and a calendar promotes accurate orientation and a normal sleep–wake cycle. In addition, to foster a sense of control and mastery of their situation, patients should be made an integral part of decision-making. In a randomized, controlled trial of 41 CCU patients, those who were given choices about family visits, daily hygiene schedule, physical activity, and their room environment enjoyed significant improvement in anxiety and depression measures after 48 hours [66]. Muscle relaxation has been used with some success in weaning patients from ventilators. In limited studies, relaxed, nonpercussion music decreased anxious symptoms and associated physiologic measures. These methods should be considered adjunctive to pharmacotherapy and may help reduce the need for medications.

Benzodiazepines represent the standard for anxiolysis in the ICU; of these, lorazepam is the most widely used. Available in an intravenous formulation, it undergoes little hepatic metabolism, has no active metabolites, and is more appropriate for use in patients with liver disease or with poor liver function. Lorazepam is also useful for long-term sedation in ventilated patients as it is not associated with heart block (as is propofol) or with wide body storage (as is midazolam). However, lorazepam is mixed with propylene glycol, and prolonged use of high doses can precipitate an osmolar-gap acidosis.

Another agent of recent interest and increasingly used in the ICU is dexmedetomidine, which inhibits the central and peripheral effects of norepinephrine and epinephrine, resulting in sedation and analgesia. While dexmedetomidine may cause bradycardia and hypotension, trial data suggest that clinically significant adverse hemodynamic changes are rare [33,34]. Dexmedetomidine and propofol performed equally in pain and anxiety reduction and sleep/rest promotion [67].

Other agents that may prove useful in the anxious patient are SSRIs, neuroleptic agents, and propofol. SSRIs have been shown to decrease the sense of dyspnea in anxious patients with COPD [68]. Neuroleptics are beneficial in patients who are fearful, delirious, or so anxious that they are nearly psychotic [69]. Use of neuroleptic agents is discussed in Chapter 197. Propofol continues to be the most commonly used medication for sedation in the ICU but is impractical for routine anxiolysis given its significant respiratory-depressant effects [70]. Table 198.4 contrasts various agents commonly used to quell anxiety in critically ill patients. Table 198.5 presents a summary of randomized trials of anxiety treatments in critically ill patients.

CONCLUSION

Ubiquitous in the ICU, anxiety has a broad range of physiologic and psychological consequences. Although it can be difficult to diagnose in the acutely ill, current evidence suggests that identification and treatment of anxiety enhance patient comfort and compliance and improve morbidity and mortality. Therefore, anxiety should be routinely assessed in critically ill patients. Psychiatric consultation should be considered whenever anxiety complicates the clinical course.

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CHAPTER 199 ■ DIAGNOSIS AND TREATMENT OF DEPRESSION IN THE INTENSIVE CARE UNIT PATIENT

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Intense emotions are evoked routinely in intensive care units (ICUs), where life-and-death decisions occur daily. In the ICU, depression can be a psychological reaction to an acute medical illness, a manifestation of a primary affective disorder, a mood disorder associated with a specific organic disease or its treatment, or a result of the confusing overlap of somatic symptoms of depression and symptoms of medical illnesses.

In this chapter, the term depression refers not to being transiently sad, discouraged, disappointed, despondent, or grief-stricken but refers to major depressive disorder (MDD), defined in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) [1] as a syndrome of distinct and persistent dysphoria associated with neurovegetative changes and functional impairment. Varied in presentation,

course, and response to treatment, depressive disorders remain a pathophysiological enigma, despite centuries of recognition and more recent investigation of their possible genetic, neurochemical, neuroanatomic, endocrine, and immune underpinnings [2,3].

Many physicians believe that depression is appropriate in the ICU because severe illness devastates a person's life. However, we believe that while being dispirited may be an understandable response to critical illness, having a depressive disorder is not; therefore, it is always important to treat the latter. In fact, compelling evidence shows that untreated depression increases morbidity and mortality from cardiac and neurologic conditions and has detrimental effects on other—perhaps all—organ systems.

In this chapter, we focus on the links between depressive and medical conditions and the diagnosis, evaluation, and treatment of depression in critically ill patients.

LINKS BETWEEN DEPRESSION AND MEDICAL CONDITIONS

Cardiovascular Disease

That depression is associated with the development and the progression of coronary heart disease (CHD), and with worse prognosis in CHD patients, is well established [4]. Not proven thus far is that treatment of depression can improve or prevent these outcomes. After two trials—the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study [5] and the Myocardial Infarction and Depression–Intervention Trial (MIND–IT) [6]—failed to show this, attention turned to isolating those attributes of a depressive episode that portend greater risk. Secondary analyses of these and other trials have examined symptom type, episode onset before or after an index event [7,8], recurrence [9,10], treatment responsiveness [11], and persistence of the cardiotoxic effects of depression [12]. For example, some studies suggested that worse cardiac outcomes are associated with somatic/affective symptoms (e.g., insomnia, fatigability, and diminished libido) more than with cognitive/affective symptoms (e.g., pessimism, self-dislike, and suicidal ideas) [13–15].

Possible explanations for the greater rates of cardiac death among patients diagnosed with depression include hypothalamic–pituitary–adrenal axis hyperactivity, elevation in inflammatory markers (e.g., interleukin 6, tumor necrosis factor α), diminished heart rate variability, decreased parasympathetic tone, increased sympathetic tone, and enhanced platelet activation causing more avid platelet aggregation and plaque formation [16]. Interestingly, sertraline decreases platelet and endothelial activation in depressed patients after an acute coronary syndrome (ACS) [17,18]. The Heart and Soul Study, a prospective cohort study of 1,017 patients with stable CHD, found that behavioral factors, especially physical inactivity, were most responsible for the greater rate of adverse cardiac events in patients with depressive symptoms [19].

Cerebrovascular Disease

As with cardiovascular disease, there appear to be bidirectional links between cerebrovascular disease and depressive illness. The Caerphilly Study of 2,201 men found that psychological distress predicted fatal stroke but not nonfatal stroke or transient ischemic attack (TIA) [20]. The Framingham Heart Study of 4,120 men and women found that depressive symptoms were a risk factor for stroke or TIA before, but not after, age 65 [21].

Poststroke depression (PSD) has been extensively studied during the past 3 decades. Robinson [22] pooled the available data and found the mean prevalence of poststroke affective illness to be 19.3% for major depression and 18.5% for minor depression. Risk factors for the development of PSD include stroke severity, extent of physical disability, presence of cognitive impairment, and poor social support [23].

In the early 1980s, Robinson et al. [24,25] reported that the severity of PSD correlated with the proximity of the lesion to the frontal pole in the left, but not the right, hemisphere. This finding has been replicated by some [26,27], but not all [28], researchers; this localization may hold only during the first few months after stroke [29].

DIAGNOSIS OF DEPRESSION

Important questions for the intensivist are "What is depression?" and "What does a patient experiencing depression look like in the ICU?" To qualify for a diagnosis of MDD according to the DSM-IV, a patient must have five of the nine symptoms listed in Table 199.1, one of which must be either depressed mood or anhedonia, most of the day, nearly every day, for at least 2 weeks. The mnemonic—SIG: E CAPS (where SIG [abbreviation for the Latin, *signa*] refers to the instructions on a prescription, E refers to energy, and CAPS refers to capsules)—is a helpful guide to remember the eight neurovegetative symptoms associated with depressed mood. The mnemonic—ABCs of depression—portrays more richly the myriad affective, behavioral, and cognitive aspects of the condition (Table 199.2). Each symptom should be asked about, and questions about suicide should be raised directly. If a patient has thoughts of suicide, he or she should be asked whether there is a specific plan; the physician should then make a judgment about the likelihood of the patient's acting on the plan. If an active plan for suicide exists, psychiatric consultation is imperative (see Chapter 200).

Four of the nine diagnostic criteria (i.e., insomnia, fatigue or loss of energy, diminished ability to think or concentrate, and anorexia or weight loss) are difficult to attribute exclusively to depression in the medically ill patient. However, in terminally ill cancer patients, Chochinov et al. [30] found that inclusion of these somatic symptoms in the diagnostic criteria did not artifactually increase rates of diagnosis, as long as the cardinal symptoms of depressed mood and anhedonia were held to the strict requirement of presence most of the day, nearly every day, for at least 2 weeks.

TABLE 199.1

SIG: E CAPS—A MNEMONIC FOR DIAGNOSTIC CRITERIA FOR MAJOR DEPRESSIVE DISORDER

Depressed mood
*S*leep, increased or decreased
*I*nterest or pleasure in activities, markedly decreased (anhedonia)
*G*uilt or feelings of worthlessness
*E*nergy, decreased
*C*oncentration, decreased
*A*ppetite or weight, increased or decreased
*P*sychomotor agitation or retardation
*S*uicidal thinking

Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC, American Psychiatric Association, 1994.

TABLE 199.2

ABCs OF DEPRESSION—AFFECTIVE, BEHAVIORAL, AND COGNITIVE FEATURES

Affective	Behavioral	Cognitive
Depressed mood	Crying	Suicidal thinking
"Blue" mood	Increased or decreased sleep	Thoughts of death
Sadness	Increased or decreased appetite	Somatic preoccupation
Blunted affect	Decreased energy	Guilty rumination
Hopelessness	Psychomotor agitation or retardation	Confusion
Emptiness	Increased or intractable pain	Decreased concentration
Irritability	Deliberate self-injury	
Anger	Impulsivity	
Decreased interest	Poor eye contact	
	Noncompliance	

Patients Who are Unable to Speak

It may be particularly difficult to diagnose depression in a patient who is being mechanically ventilated or who has aphasia. However, much can be learned about a patient even when he or she is mute. It is important to watch facial expressions, observe hand gestures and other body language, and read lips. An individual who averts his or her eyes from the examiner's gaze may be demoralized, discouraged, or depressed. Slow, sighing respirations may indicate depression rather than respiratory insufficiency. The astute clinician can also watch vital-sign monitor screens, looking for changes that can signify intense affect.

Does the patient respond to the mention of a favorite hobby or a grandchild with a smile or with tears? Is the patient's affect labile or consistent with the content of the discussion? Emotional lability is not usually an indicator of MDD; instead, it suggests frontal lobe dysfunction. One can probe for affect by joking and observing the patient's reaction.

A patient who can move his or her arms can be asked to write, draw, or point to a letter or a picture board. One simple screening test that can be used is human figure drawing (i.e., having the patient draw a picture of a person and another of what the patient thinks is wrong with the person). Typically, drawings by depressed patients convey their sense of dejection or a disordered understanding of their dilemma.

TABLE 199.3

METHODS OF ASSESSING DEPRESSION IN SENSORIALLY COMPROMISED PATIENTS

- Watch facial expressions and gestures
- Write questions
- Have patients write answers
- Use letter or picture board
- Observe whether facial expressions are consistent with content of discussion
- Observe rate of change of affect
- Ask about and observe neurovegetative features of depression
- Ask about known sources of the patient's enjoyment (e.g., favorite hobby, grandchildren, sports) and observe whether the patient takes pleasure in these things
- Joke with the patient or tell a funny story and observe the patient's reaction
- Ask the patient to draw a picture of himself or herself and what is wrong, then assess the pictures for a sense of demoralization or hopelessness
- Make a fist and ask the patient, "What would you do if you had one of these?", and assess emotions in response to this maneuver

Some tracheostomized patients may have the oxygenation status, control of respiratory muscles, and ability to manage secretions sufficient to use a Passy-Muir valve, which permits exhaled air to pass the larynx and thus allows the patient to speak. Alternatively, electronic voice-output communication aids may be used. These devices pair prerecorded messages or synthesized speech with labeled icons; patients communicate messages by touching buttons on display screens or on touch-sensitive keyboards. Speech pathologists have knowledge of and access to such technology. Methods of assessing depression in sensorially compromised patients are summarized in Table 199.3.

DIFFERENTIAL DIAGNOSIS OF DEPRESSION

Causes Related to Medical Conditions

A variety of medical illnesses can cause affective disorders, contribute to their occurrence, and worsen their severity (Table 199.4). Clues that depression is due to a medical illness include

TABLE 199.4

MEDICAL CONDITIONS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

- Cardiovascular
  - Cardiac tumors
  - Congestive heart failure
  - Hypertensive encephalopathy
- Collagen-vascular
  - Polyarteritis nodosa
  - Systemic lupus erythematosus
- Endocrine
  - Diabetes mellitus
  - Hyper- or hypoadrenalism
  - Hyper- or hypoparathyroidism
  - Hyper- or hypothyroidism
- Infectious
  - Hepatitis
  - Human immunodeficiency virus
  - Mononucleosis
  - Influenza
- Metabolic
  - Acid–base problems
  - Hypokalemia
  - Hyper- or hyponatremia
  - Renal failure
- Neoplastic
  - Carcinoid
  - Pancreatic carcinoma
- Neurologic
  - Brain tumor
  - Multiple sclerosis
  - Parkinson's disease (especially with on/off phenomenon)
  - Temporal lobe epilepsy
  - Stroke
  - Subcortical dementia
- Nutritional
  - Vitamin B_{12} deficiency
  - Wernicke's encephalopathy

older age at onset of symptoms, lower incidence of a family history of depression, and changes in personality and cognition. A thorough history (including a review of systems), physical (including neurologic) examination, and laboratory testing can distinguish between primary (i.e., due to a psychiatric condition) and secondary (i.e., due to a medical condition) causes of depression. For secondary causes, treatment of the underlying illness is usually more effective than is the use of psychotropic medications.

Perhaps the most important differential diagnosis to consider in a patient who appears to have MDD is hypoactive delirium. The key feature that distinguishes it from depression is inattention (i.e., an inability to focus and sustain alertness on a given stimulus and to resist distraction by other stimuli). Delirium is discussed in Chapter 197.

Causes Related to Medical Treatments

The pharmacologic agents most often responsible for depression in the ICU are antihypertensives, beta-blockers, antiarrhythmics, and steroids (Table 199.5). Some medications may cause depression only after several weeks or even months of continuous use. If a drug regimen or a dosage increase appears to be temporally related to the patient's depression, the dose should be lowered or the medication eliminated entirely. If the medication cannot be stopped without serious risk to the patient, the depression should be treated.

Steroids

Depression, mania, psychosis, and delirium are frequent side effects of corticosteroid therapy. Mood symptoms are dose-dependent and usually occur within the first 2 weeks of therapy, although they can arise on the first day. A practical rule of thumb holds that neuropsychiatric adverse effects are common with prednisone ≥80 mg per day (or equivalent), uncommon ≤30 mg per day, and not uncommon in between. Although it has been suggested that women are more likely to develop steroid-induced adverse effects, the apparent increased frequency may be due to the higher prevalence of rheumatologic diseases in women. Corticosteroid-induced mood disorders are generally reversible with dosage reduction or discontinuation of the medication.

TABLE 199.5

DRUGS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

Acyclovir (especially at high doses)
Alcohol
Amphetamine-like drugs (withdrawal): fenfluramine, phenmetrazine, phenylpropanolamine
Anabolic steroids: methandrostenolone, methyltestosterone
Anticonvulsants (at high doses or plasma levels): carbamazepine, phenytoin, primidone
Antihypertensives: clonidine, hydralazine, methyldopa, reserpine, thiazides
Asparaginase
Baclofen
Barbiturates
Benzodiazepines: alprazolam, clonazepam, clorazepate, diazepam, lorazepam, triazolam
Beta-blockers: atenolol, betaxolol, propranolol, timolol
Bromides
Bromocriptine
Cimetidine
Cocaine (withdrawal)
Oral contraceptives
Corticosteroids
Cycloserine
Dapsone
Digitalis (at high doses or in elderly patients)
Diltiazem
Disopyramide
Ethionamide
Halothane (postoperatively)
Heavy metals
Histamine-2 receptor antagonists: cimetidine, ranitidine
Interferon α
Isoniazid
Isotretinoin
Levodopa (especially in the elderly)
Mefloquine
Metoclopramide
Metrizamide
Metronidazole
Nalidixic acid
Narcotics: meperidine, methadone, morphine, pentazocine, propoxyphene
Nifedipine
Nonsteroidal anti-inflammatory drugs
Norfloxacin
Phenylephrine
Prazosin
Procaine derivatives: lidocaine, penicillin G procaine, procainamide
Thyroid hormones
Trimethoprim-sulfamethoxazole

LABORATORY EVALUATION OF DEPRESSION

Although the clinical interview and mental status examination are the most important components of psychiatric diagnosis, the use of laboratory tests is essential to exclude organic causes of depression. Although there is no consensus on the laboratory tests necessary in a patient with new-onset mood disorder, Table 199.6 lists those tests that should be considered. Thyroid-stimulating hormone is not on this list because many critically ill patients have abnormal thyroid biochemical profiles but do not have intrinsic thyroid disease. Syphilis and hypovitaminosis are rarely the sole causes of depression; tests for these conditions should be ordered only when there is a specific indication for them. Neuroimaging, electroencephalography, and cerebrospinal fluid analysis are relatively indicated in patients with new-onset psychiatric symptoms, altered cognition, new neurologic symptoms, seizures, and fever. The more of these features a patient has, the more important these additional tests become.

TREATMENT OF DEPRESSION

Patients who meet the criteria for MDD are usually treated with a somatic therapy (including pharmacotherapy and electroconvulsive therapy [ECT]), alone or in combination with psychotherapy (Table 199.7). In critical care units, somatic therapies are the most widely used treatments for depression. Pharmacotherapy may be used in critical care units also for patients who have an adjustment disorder with depressed mood, particularly when these patients have several neurovegetative symptoms. A patient who is neither eating nor sleeping and who lacks the energy to participate in his or her rehabilitation may be helped considerably by antidepressants, especially psychostimulants.

Each type of pharmacotherapy has its own indications and contraindications, but general rules are available when

TABLE 199.6

LABORATORY EVALUATION OF DEPRESSION

Complete blood count with differential
Complete blood chemistries
Serum and urine toxicology
Urinalysis
Vitamin B_{12}
Folate
Rapid plasma reagin
Neuroimaging
Electroencephalogram
Cerebrospinal fluid analysis

selecting an antidepressant [31,32]. The most common rule is to choose a medication with a side-effect profile that best fits a patient's needs. For instance, a patient who is having trouble sleeping will benefit from a sedating antidepressant. Conversely, a patient who has severe psychomotor retardation may benefit from a more stimulating antidepressant. With the exception of the psychostimulants, all antidepressants require approximately 4 to 6 weeks until full antidepressant effects are noted, although some response can occur in 1 to 2 weeks. Obviously, in critical care units, quicker effects are generally needed. Stimulants and ECT work more quickly, usually within several days. Patients with depression may also manifest considerable anxiety and may be helped by the use of an anxiolytic while awaiting response to an antidepressant. Psychotically depressed patients (with delusions or hallucinations) may need antipsychotics for control of symptoms.

Psychostimulants

Psychostimulants have been used to treat depressive symptoms since their development in the 1930s, but they fell into disrepute when they became known as drugs of abuse in the 1950s and 1960s. Since then, there have been numerous reports on the use of stimulants in the treatment of depressed patients, particularly apathetic and geriatric patients; recently, there has been a renewed interest in the use of psychostimulants in depressed, medically ill patients who are intolerant of other medications

TABLE 199.7

COMPARATIVE PROPERTIES OF SOME ANTIDEPRESSANTS

Drug	Metabolism	ACh	Sedation	OH	Cardiac arrhythmia	Seizure risk	Target dose range (mg/d)	Drug interactions
Stimulants	Renal	0	0	0	Rare	Rare	5–20	
SSRIs								Risk of serotonin syndrome
Citalopram	Hepatic	+	+	+	Rare	Rare	20–60	Relatively few
Escitalopram	Hepatic	0–+	0–+	0–+	Rare	Rare	10–30	Relatively few
Fluoxetine	Hepatic	+	+	+	Rare	Rare	≥20	Increased levels of TCAs
Fluvoxamine	Hepatic	+	+	+	Rare	Rare	50–250	
Paroxetine	Hepatic	+	+	0	Rare	Rare	≥20	
Sertraline	Hepatic	0	0	0	Rare	Rare	50–200	
SNRIs								Risk of serotonin syndrome
Duloxetine	Hepatic	+	+	0–+	Rare	Rare	30–90	
Venlafaxine	Hepatic	0	0	0	Rare	Rare	150–300	
TCAs								
Amitriptyline	Hepatic	+ + +	+ + +	+ + +	Yes	Increased	≥150	
Amoxapine	Hepatic	+	++	+	Yes	Increased	≥200	
Desipramine	Hepatic	+	+	+ + +	Yes	Increased	≥150	
Doxepin	Hepatic	++	+ + +	++	Yes	Increased	≥200	
Imipramine	Hepatic	++	++	+ + +	Yes	Increased	≥200	
Maprotiline	Hepatic	+	+ + +	+	Yes	Increased	≥150	
Nortriptyline	Hepatic	++	++	+	Yes	Increased	≥100	
Protriptyline	Hepatic	+ + +	+	++	Yes	Increased	≥30	
MAOIs	Hepatic	0	+	+ + +	Rare	Rare	45–90	Hypertensive crisis with tyramine or sympathomimetics; avoid narcotics
Others								
Bupropion	Hepatic	+	0	0	Rare	Increased	IR, 200–300; SR/XL, 150–300	
Mirtazapine	Hepatic	+	+ + +	+	Rare	Rare	30–45	
Trazodone	Hepatic	0	+ + +	++	Yes	Increased	≥150	Digitalis toxicity

+, low; ++, moderate; + + +, high; ACh, anticholinergic effects; IR, immediate release; MAOIs, monoamine oxidase inhibitors; OH, orthostatic hypotension; SNRIs, serotonin–norepinephrine reuptake inhibitors; SR, sustained release; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; XL, extended release.

Adapted, in part, from Mann JJ: The medical management of depression. *N Engl J Med* 353:1819, 2005.

[33]. Thought to be particularly effective in patients with cancer and stroke, their rapid onset is of great use in any setting, including the ICU, where speed of recovery is crucial. For example, they are valuable in patients who are difficult to wean from mechanical ventilation [34].

The psychostimulants most commonly used are dextroamphetamine (Dexedrine) and methylphenidate (Ritalin). Both appear to work through the direct neuronal release of dopamine and norepinephrine; dextroamphetamine blocks catecholamine reuptake and weakly inhibits monoamine oxidase. Both of these psychostimulants are predominantly excreted by the kidneys, although dextroamphetamine also undergoes a complex biotransformation.

The usual effects of stimulants are to increase motor behavior, increase arousal, and decrease appetite; however, in patients who are anorexic on the basis of depression, appetite is paradoxically increased, likely through dopaminergic stimulation of the nucleus accumbens. Their antidepressant effect is usually evident in the first 2 days of treatment, if not earlier. In a review of 66 patients hospitalized on medical-surgical wards at Massachusetts General Hospital, 93% achieved maximum benefit within 2 days of use [35,36]. Stimulants do not show anticholinergic effects or cause orthostatic hypotension. They can increase heart rate and blood pressure and can cause coronary spasm and cardiac arrhythmias; however, these effects are rare (even with preexisting cardiac abnormalities) at the low doses (5 to 20 mg/day) usually used for the treatment of depression [35]. In fact, stimulants have been used safely and effectively in a broad spectrum of patients, including those with critical illness, and have shown little potential for abuse or dependence. Contraindications to stimulant use include the concurrent use of α-methyldopa (which becomes a sympathoamine when metabolized), monoamine oxidase inhibitors (MAOIs), and bronchodilators; and pregnancy, seizures, delirium, psychosis, significant hypertension, and active angina [37].

Psychostimulants should be the first consideration in treating depression in critically ill patients. Patients are started on 5 mg of methylphenidate or 2.5 to 5 mg of dextroamphetamine in the morning. The dose is increased by 5 mg per day (for methylphenidate) or 2.5 to 5 mg per day (for dextroamphetamine) until a therapeutic effect is detected or until a maximum dose of 20 mg has been reached. Heart rate and blood pressure should be monitored as closely as necessary. Stimulants are usually given for at least 1 to 2 weeks after depressive symptoms have fully remitted. In most cases, after stimulants are stopped, depression does not recur.

Stimulants taken in overdose may cause seizures, coma, hallucinations, paranoia, hyperthermia, hypertension, cardiac arrhythmias, angina, and circulatory collapse. The major treatment for overdose is to acidify the urine (which enhances renal excretion) and to use supportive measures for all other abnormalities.

Modafinil (Provigil)—a wakefulness-promoting medication approved for narcolepsy, shift work sleep disorder, and obstructive sleep apnea/hypopnea syndrome—may be a beneficial alternative to the psychostimulants.

Selective Serotonin Reuptake Inhibitors

The SSRIs are a class of antidepressants that causes a potent and selective blockade of serotonin reuptake. Since the introduction of fluoxetine (Prozac) in 1987, SSRIs have become the most widely prescribed class of antidepressants. Other SSRIs include sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro). They are far less anticholinergic, antihistaminergic, and anti-α_1-adrenergic than the older tricyclic antidepressants (TCAs) and, therefore, are associated with far fewer side effects. They also have fewer cardiovascular effects and do not commonly cause orthostatic hypotension.

Pharmacokinetics

SSRIs are well absorbed from the gastrointestinal tract, and absorption is generally unaffected by food and antacids. They have a large volume of distribution and are highly protein-bound. They are extensively metabolized in the liver, where they are oxidized, methylated, and conjugated. The elimination half-lives of sertraline, paroxetine, fluvoxamine, and citalopram are approximately 1 day (although sertraline has a mildly active metabolite with a half-life of 66 hours); this allows once-a-day dosing. Fluoxetine has a half-life of 2 to 3 days and a highly active metabolite (norfluoxetine) with a mean half-life of 6.1 days. Fluoxetine takes a much longer time to reach steady state and, more importantly for drug overdoses, can take weeks to months to be fully cleared. Elimination half-lives are dose-dependent (i.e., higher doses and lengthier usage are associated with higher plasma levels and longer half-lives). SSRIs show wide interindividual variation in pharmacokinetics and do not yet have a clearly established dose-response curve.

Metabolic Impairment

Fluoxetine, sertraline, fluvoxamine, and citalopram are unaffected by renal dysfunction [38,39]. Paroxetine, although minimally excreted in the urine (like other SSRIs), shows increased plasma concentrations in the setting of renal disease [38]. Fluoxetine, sertraline, paroxetine, and citalopram doses should be reduced by at least half in patients with liver disease [38]. Fluvoxamine has been used in patients with cirrhosis and hepatic encephalopathy without adverse effects [40]. The hepatic clearance, not the plasma concentration, of fluvoxamine is affected by cirrhosis. Therefore, the dosage frequency, rather than the total dosage, should be altered [40]. In elderly individuals, fluoxetine does not have altered pharmacokinetics; in contrast, sertraline and paroxetine have increased plasma levels and slower clearance. Although citalopram has a 30% longer half-life in the elderly, the frequency and severity of side effects are not higher in this group [41].

Side Effects

SSRIs can cause tremulousness, agitation, irritability, insomnia, anorexia, nausea, vomiting, diarrhea, excess sweating, and sexual dysfunction (i.e., decreased libido, erectile and orgasmic dysfunction). The syndrome of inappropriate antidiuretic hormone is an uncommon adverse effect reported with all of the SSRIs; especially in critically ill patients, other causes of hyponatremia should be sought before attributing the metabolic derangement to the SSRI. The SSRIs do not typically cause clinically significant changes in heart rate, blood pressure, or the electrocardiogram (ECG). Overdoses of SSRIs are discussed in Chapter 124.

Theoretically, SSRIs can cause angina or myocardial infarction (MI) due to the direct vasoconstrictive effects of serotonin on damaged myocardium. When fluoxetine therapy is initiated, serum serotonin levels rise for the first 2 weeks and then return to baseline. This mechanism has been implicated in 3 cardiac deaths that occurred 10 days after initiation of fluoxetine [42]. This theoretical concern should extend to other SSRIs as well.

Drug–Drug Interactions

The SSRIs are extensively metabolized by the cytochrome P450 system. All of them also inhibit various isoenzymes in this system and consequently raise the plasma levels of other drugs metabolized by those isoenzymes; sertraline, citalopram, and escitalopram do this the least. The interactions most likely to

TABLE 199.8

SELECTED SUBSTRATES AND INHIBITORS OF CYTOCHROME P450 ISOENZYMES

1A2	2C	2D6	3A3/4
		Substrates	
Acetaminophen	Barbiturates	Codeine	Amiodarone
Aminophylline	Diazepam	Encainide	Astemizole
Haloperidol	Mephenytoin	Flecainide	Calcium-channel blockers
TCAs	Omeprazole	Haloperidol	Cisapride
Theophylline	Phenytoin	Hydrocodone	Diazepam
	Propranolol	Metoprolol	Disopyramide
	TCAs	Propafenone	Lidocaine
		Propranolol	Loratadine
		TCAs	Macrolide antibiotics
		Timolol	Omeprazole
			Propafenone
			Quinidine
			Steroids
			Terfenadine
			TCAs
		Inhibitors	
Fluoxetine	Fluoxetine[a]	Fluoxetine[a]	Fluoxetine
Fluvoxamine[a]	Fluvoxamine[a]	Paroxetine[a]	Fluvoxamine[a]
Paroxetine	Sertraline	Sertraline	Nefazodone[a]
			Sertraline

[a]Strong inhibitor.
TCAs, tricyclic antidepressants.

occur in an ICU are listed in Table 199.8. Attention to drug dosage can mitigate the harmful effects of these interactions.

Drug Discontinuation

The usually mild symptoms of the SSRI discontinuation syndrome (e.g., headache, dizziness, myalgias, and nausea) are generally eclipsed by more pressing issues in critically ill patients.

Atypical Antidepressants

Bupropion

A monocyclic ketone antidepressant, bupropion (Wellbutrin) blocks norepinephrine and dopamine reuptake. As such, it can be activating and used in place of psychostimulants for patients who cannot tolerate these agents or in whom they are contraindicated. Its major side effects are agitation, insomnia, tremulousness, nausea, vomiting, and diarrhea. The immediate-release formulation is associated with an increased risk of seizures, but this risk in the sustained-release (SR) and extended-release (XL) preparations is comparable to that associated with other antidepressants. It carries a low risk of cardiac toxicity, though, in overdose, sinus tachycardia and intraventricular conduction delays have been reported [43]. Bupropion has gained widespread use as an aid to smoking cessation.

Mirtazapine

Mirtazapine (Remeron) is an analog of the tetracyclic antidepressant, mianserin. As an antagonist at presynaptic and postsynaptic α_2-adrenergic receptors and at postsynaptic 5-HT_2 and 5-HT_3 receptors, it enhances both norepinephrine and serotonin transmission. It has few anticholinergic and anti-α_1-adrenergic effects. Mirtazapine is a potent histamine blocker and can cause significant sedation, an increase in appetite, and weight gain—a side-effect profile that is often exploited to advantage in medically ill patients. Mirtazapine is devoid of significant effects on the cytochrome P450 system, making it less apt to cause drug–drug interactions.

Venlafaxine

Venlafaxine (Effexor) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). It is very similar to the SSRIs in most clinical and pharmacologic aspects. It has few anti-α_1-adrenergic, anticholinergic, and antihistaminergic side effects. Venlafaxine has a 6- to 8-hour half-life and must be given 2 to 3 times daily, but an extended-release preparation (Effexor XR) allows once-daily dosing. It causes a dose-dependent increase in systolic and diastolic blood pressure (up to 7.5 mm Hg), occurring in approximately 7% of patients taking daily doses between 200 and 300 mg and in up to 13% of patients taking > 300 mg [44]. The major active metabolite of venlafaxine, desvenlafaxine, is now available as a primary compound (Pristiq); its advantages over its parent compound are uncertain.

Duloxetine

Another SNRI, duloxetine (Cymbalta) is indicated for MDD, generalized anxiety disorder, diabetic neuropathy, and fibromyalgia. Its half-life is 12 hours, and it can be given once or twice daily. Like venlafaxine, it has little effect on α_1-adrenergic, cholinergic, and histaminergic receptors. Any therapeutic advantage over venlafaxine, particularly in critically ill patients, has yet to be demonstrated.

Trazodone

A triazolopyridine derivative, trazodone (Desyrel) is an atypical antidepressant usually used as a sleep aid. It has a more

benign cardiac profile than the TCAs and rarely causes cardiac dysrhythmias. The most common cardiovascular effect of trazodone is orthostatic hypotension. Priapism is a rare adverse event.

Tricyclic Antidepressants

TCAs work by blocking reuptake of norepinephrine and serotonin at presynaptic sites. The most common side effects of TCAs are sedation, orthostatic hypotension, and anticholinergic effects (including confusion, blurred vision, dry mouth, constipation, and urinary hesitancy or retention). The tertiary-amine parent compounds, amitriptyline (Elavil) and imipramine (Tofranil), are more apt to produce these adverse effects than are their respective secondary-amine metabolites, nortriptyline (Pamelor) and desipramine (Norpramin).

Because of this extensive side-effect profile, including adverse effects on cardiac conduction and cardiac rhythm, the TCAs have largely been eclipsed in recent times by the SSRIs and other newer agents, which are safer and better tolerated. For example, in a head-to-head comparison of nortriptyline and fluoxetine in patients with cardiac disease, patients taking nortriptyline had 5 times the incidence of adverse cardiac effects compared to those in the fluoxetine group (20% vs. 4%) [45]. TCAs are relatively contraindicated in patients with cardiac disease and are not recommended in the acute post-MI period. In fact, some data even suggest that TCAs may precipitate arrhythmias and sudden death in cohorts other than just the post-MI population [46].

As a result, it is relatively unusual to see a patient on a TCA at an antidepressant dose in the ICU and highly unusual to start a TCA in an ICU patient. TCAs are still used with some regularity for neuropathic pain syndromes; when used in this situation, doses are much lower than those used in depression treatment. Overdoses with TCAs may be treated in the ICU and are discussed in Chapter 123.

Monoamine Oxidase Inhibitors

The MAOIs (isocarboxazid [Marplan], phenelzine [Nardil], tranylcypromine [Parnate]) work by blocking the oxidative deamination of biogenic amines (e.g., norepinephrine, serotonin) and have been used for the treatment of depression since the 1950s. MAOIs may cause a profound hypertensive crisis when a patient taking MAOIs also takes a sympathomimetic medication (e.g., reserpine, guanethidine, pseudoephedrine, and ephedrine) or ingests tyramine-containing foods (e.g., aged cheeses, pickled foods, and yeast extracts). Coadministration with opioids, particularly meperidine, also may lead to hypertensive crises and to elevated blood levels of meperidine and its neurotoxic metabolite, normeperidine. The use of beta-blockers with MAOIs may lead to unopposed α-adrenergic activity and also cause severe hypertension. For these reasons, similar to TCAs, MAOIs are infrequently used in recent times, even by psychiatrists, and it would be highly unusual to begin an MAOI in an ICU patient. Overdoses with MAOIs may be treated in the ICU and are discussed in Chapter 123.

Pharmacologic Treatment of Depression in Heart Disease

Several studies have examined the effect of antidepressant treatment on psychiatric or cardiovascular outcome or both in patients with CHD. These include the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), ENRICHD, MIND–IT, and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. The basic details and findings of these landmark studies, as well as two other randomized trials [47,48], are summarized in Table 199.9.

In SADHART, response to sertraline was independently predicted by each of the following factors: (a) onset of the current depressive episode before the ACS, (b) a history of MDD, and (c) greater severity of depression [49]. Moreover, in the cohort with recurrent MDD, quality of life and several functional status scores were significantly improved in the sertraline group [50]. SADHART was designed to evaluate only the safety and efficacy of sertraline, not its effect on cardiac outcomes. Nevertheless, the number of severe cardiac events (e.g., death, MI, congestive heart failure [CHF], recurrent angina, stroke) was lower in patients treated with sertraline (14.5%) compared with those receiving placebo (22.4%) [51]. After a median follow-up of almost 7 years, baseline MDD severity and persistence of depression despite active or placebo treatment in the 6 months immediately after ACS independently predicted more than a doubling of mortality risk [7].

ENRICHD was the first trial of the effect of depression treatment on mortality and reinfarction in post-MI patients [5]. The differential improvement in depression between the intervention and the usual-care groups was only modest and was short-lived. Most notably, the intervention yielded no cardiac benefit. This negative result may have occurred because many of the patients in the usual-care arm received antidepressant medication, thus potentially obscuring any between-group differences. In fact, a secondary analysis found that patients exposed to SSRIs had a lower risk of death or recurrent MI and of all-cause mortality compared to patients who did not take SSRIs [52]. In addition, patients with mild, transient depressions likely to have improved on their own were included in the study, and the treatment duration of 6 months may have been too short to discern a salutary effect.

Thus Carney et al. [53] undertook a subgroup analysis of patients with full (rather than modified) criteria for MDD or minor depression, a baseline Beck Depression Inventory (BDI) score ≥ 10, and a history of at least one episode of MDD and completed the follow-up evaluation 6 months after enrollment (i.e., those patients who completed the intervention). While the difference in the mean change in BDI score from baseline to 6 months between groups was higher in this narrowed sample than in the entire cohort, this enhanced improvement did not translate into a survival benefit. While patients who responded to the intervention experienced a reduction in mortality, the authors recommended caution in evaluating this finding as it was based on small numbers.

MIND–IT examined the effects of antidepressant treatment on cardiac prognosis and on the long-term course of depression [6]. The active treatment arm included three possibilities: randomization to mirtazapine or placebo, open treatment with citalopram, or treatment at the discretion of the treating psychiatrist. Those randomized to mirtazapine or placebo were given the option to switch to unblinded citalopram if there was no response after 8 weeks. Similar to ENRICHD, no significant differences between active treatment and usual care were found in depressive or cardiac outcome. In a separate analysis of just the patients who received mirtazapine, this agent yielded a therapeutic advantage over placebo [54]. In a three-way comparison of responders and nonresponders to either antidepressant (mirtazapine or citalopram) and patients who received no treatment, responders had the least cardiac events, followed by the untreated patients and then the nonresponders, leading the authors to suggest that persistence of depression may be the crucial "cardiotoxic" attribute of depressive illness, for which treatment resistance may be a marker [55].

TABLE 199.9

RANDOMIZED, CONTROLLED TRIALS OF DEPRESSION PHARMACOTHERAPY IN PATIENTS WITH CARDIOVASCULAR DISEASE

Study	Enrollment	Intervention	Results
Berkman et al. [5]	2,481 patients with modified[a] DSM-IV major or minor depression and/or low perceived social support within 28 d after MI	Intervention (CBT ± sertraline 50–200 mg/d or other medication) vs. usual care for 6 mo	The intervention yielded a significant, though modest, improvement in depression and in social support after 6 mo. This effect was insignificant for depression after 30 mo and for social support after 42 mo. There was no significant difference between groups in death or nonfatal MI, all-cause mortality, cardiac mortality, or recurrent nonfatal MI after an average follow-up of 29 mo.
van Melle et al. [6]	331 patients with ICD-10 depression 3–12 mo after MI	Intervention (mirtazapine, citalopram, or nonpharmacological treatment) vs. usual care for 6 mo	There was no difference between groups in mean BDI scores, presence of depression, and incidence of cardiac events at 18 mo.
Roose et al. [47]	81 patients with MDD and stable ischemic heart disease	Paroxetine 20–30 mg/d vs. nortriptyline for 6 wk	61% of the patients on paroxetine improved compared to 55% of those on nortriptyline. Those on SSRI had fewer adverse cardiac events.
Strik et al. [48]	54 patients with MDD 3–12 mo after a first MI	Fluoxetine vs. placebo	The response rate in the fluoxetine group was significantly greater at week 25, especially in patients with mild depression. There was no decrease in cardiac function in the fluoxetine group.
Glassman et al. [51]	369 patients with MDD and ACS (either MI or unstable angina)	Sertraline 50–200 mg/d vs. placebo for 24 wk	Sertraline had no significant effect on mean LVEF, increase in PVCs, QTc prolongation, and other cardiac measures. In cohorts with recurrent or severe MDD, depression scores were significantly lower in the sertraline group.
Honig et al. [54]	91 patients with DSM-IV depression 3–12 mo after MI	Mirtazapine vs. placebo for 24 wk	Mirtazapine was superior to placebo on two of three depression scales at 8 and 24 wk. There was no assessment of effect on cardiac outcomes.
Lespérance et al. [56]	284 patients with DSM-IV MDD and CAD	Twelve weekly sessions of IPT with CM vs. CM alone, and citalopram 20–40 mg/d vs. placebo for 12 wk	The addition of IPT to clinical management conferred no therapeutic advantage. Citalopram was significantly more effective than placebo in reducing depression.

[a] Symptoms of ≥ 7 days' duration if there was ≥ 1 prior depressive episode, 14 days if not.
ACS, acute coronary syndrome; BDI, Beck Depression Inventory; CBT, cognitive-behavioral therapy; CM, clinical management; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; ICD-10, *International Classification of Diseases*, 10th edition; IPT, interpersonal therapy; LVEF, left ventricular ejection fraction; MDD, major depressive disorder; MI, myocardial infarction; PVCs, premature ventricular contractions; QTc, QT interval corrected for heart rate; SSRI, selective serotonin reuptake inhibitor.

CREATE, the first and only study designed to evaluate paired psychological and pharmacological interventions for depression treatment in CHD patients, failed to show a therapeutic advantage for interpersonal therapy, a manualized, short-term therapy focused on loss, grief, life transitions, interpersonal conflicts, and social isolation [56]. It demonstrated, however, that citalopram is an effective antidepressant in this population.

Several additional studies in this area are currently underway. The Safety and Efficacy of Sertraline for Depression in Patients with CHF (SADHART–CHF) study will evaluate the effects of 12 weeks of sertraline compared to placebo on depression and cardiac prognosis in approximately 500 patients with MDD and chronic systolic heart failure [57]. The Bypassing the Blues (BtB) study will randomize 450 patients after coronary artery bypass grafting (CABG) to either an 8-month nurse-delivered telephone-based collaborative care intervention or usual care and evaluate the effect on mood, cardiac morbidity, health-related quality of life, and other outcomes [58]. The first study of the prevention of depression in CHD patients, the Depression in Coronary Artery Disease (DECARD) trial will randomize 240 patients with ACS, but without depression, to 1 year of escitalopram or placebo [59].

Pharmacologic Treatment of Depression in Stroke

Table 199.10 summarizes findings from the randomized, controlled trials of depression treatment and prophylaxis in patients with cerebrovascular disease [60–79]. In a randomized, double-blind, placebo-controlled study of poststroke patients, nortriptyline was more effective than fluoxetine or placebo

TABLE 199.10

RANDOMIZED, CONTROLLED TRIALS OF DEPRESSION PHARMACOTHERAPY IN PATIENTS WITH CEREBROVASCULAR DISEASE

Study	Enrollment	Intervention	Results
Lauritzen et al. [60]	20 poststroke patients with depression	Imipramine and mianserin[a] vs. desipramine and mianserin for 6 wk	The imipramine arm was superior to the desipramine arm.
Rampello et al. [61]	31 patients with "retarded" depression within 12 mo after CVA	Reboxetine[b] 4 mg twice daily vs. placebo for 16 wk	Reboxetine showed good efficacy, safety, and tolerability. There was a significant difference in change in HDRS and BDI scores between groups.
Robinson et al. [62]	159 patients with MDD 10 d to 3 mo after CVA	Nefiracetam[c] 600 or 900 mg/d vs. placebo	Both arms showed response rates > 70% and remission rates > 40%. Patients in the top quintile of HDRS scores showed a significant effect with 900 mg compared to 600 mg or placebo.
Robinson et al. [63]	104 poststroke patients with and without depression	Nortriptyline 25–100 mg/d, fluoxetine 10–40 mg/d, or placebo for 12 wk	Nortriptyline resulted in a significantly higher response than fluoxetine or placebo in reversing depression, reducing anxiety, and improving functional status. Neither active treatment improved cognitive or social functioning in depressed or nondepressed patients.
Wiart et al. [64]	31 poststroke patients with MDD	Fluoxetine 20 mg/d vs. placebo for 6 wk	Fluoxetine produced a significant improvement in depression but not in motor, cognitive, or functional scores.
Fruehwald et al. [65]	50 poststroke patients with depression	Fluoxetine 20 mg/d vs. placebo for 3 mo	Both groups showed significant improvement, with no between-group difference, after 1 mo. At 18 mo, the fluoxetine group had significantly less depression.
Choi-Kwon et al. [66]	152 patients 3–28 mo after CVA with depression, emotional incontinence, or anger proneness	Fluoxetine 20 mg/d vs. placebo for 3 mo	Fluoxetine produced significantly higher scores in the mental health, general health, and social functioning domains of QOL after 12 mo.
Li et al. [67]	150 poststroke patients with moderate to severe depression	FEWP[d] vs. fluoxetine vs. placebo for 8 wk	The active arms showed a higher clinical response than placebo, but no difference between FEWP and fluoxetine was discernible at the end of the study.
Choi-Kwon et al. [68]	152 poststroke patients with depression, emotional incontinence, or anger proneness	Fluoxetine 20 mg/d vs. placebo for 3 mo	Fluoxetine significantly improved emotional incontinence and anger proneness but not depression.
Andersen et al. [69]	66 patients with depression 2–52 wk after CVA	Citalopram 10–40 mg/d vs. placebo for 3 and 6 wk	Citalopram yielded greater improvement than placebo.
Rampello et al. [70]	74 poststroke patients with depression	Citalopram 20 mg/d vs. reboxetine 4 mg/d for 16 wk	Both agents showed good safety and tolerability. Citalopram showed a greater effect on anxious depression, reboxetine on retarded depression.
Cravello et al. [71]	50 poststroke patients with depression	Venlafaxine SR 75–150 mg/d vs. fluoxetine 20–40 mg/d for 8 wk	Both agents yielded similar improvement in depressive symptoms. Venlafaxine showed more improvement on an alexithymia scale.
Grade et al. [72]	21 poststroke patients admitted to a rehabilitation facility	Methylphenidate 5–30 mg/d vs. placebo for 3 wk	Methylphenidate yielded lower HDRS and Zung[e] scores.
Murray et al. [73]	123 poststroke patients with MDD or minor depression	Sertraline 50–100 mg/d vs. placebo for 26 wk	Both groups improved substantially. There was no difference in depression between groups and significantly less emotional distress and better QOL in the treatment group.
Narushima et al. [74]	48 poststroke patients who were not depressed at baseline	Nortriptyline 25–100 mg/d, fluoxetine 10–40 mg/d, or placebo for 12 wk for prophylaxis	Significantly fewer depressive episodes occurred in the treatment groups. However, more nortriptyline-treated patients developed depression in the 6 months after treatment was stopped compared to the other two groups.
Robinson et al. [75]	176 patients without depression within 3 mo after CVA	Escitalopram vs. placebo vs. problem-solving therapy for 1 y for prophylaxis	Patients who received either escitalopram or therapy were significantly less likely to develop depression. In an intention-to-treat analysis, escitalopram, but not therapy, was significantly superior to placebo in depression prevention.

(*continued*)

TABLE 199.10

CONTINUED

Study	Enrollment	Intervention	Results
Niedermaier et al. [76]	70 poststroke patients who were not depressed	Mirtazapine 30 mg/d vs. placebo for 1 y for prophylaxis and treatment	Significantly fewer patients in the treatment group developed depression. Fifteen out of 16 patients who developed depression were treated effectively with mirtazapine.
Rasmussen et al. [77]	137 poststroke patients who were not depressed at baseline	Sertraline 50–150 mg/d vs. placebo for 1 y for prophylaxis	Significantly fewer patients in the sertraline group developed depression compared to the placebo group.
Almeida et al. [78]	111 patients without depression < 2 wk after CVA	Sertraline 50 mg/d vs. placebo for 24 wk for prophylaxis	There was no significant difference in development of depressive symptoms.
Palomäki et al. [79]	100 patients with acute ischemic CVA	Mianserin 60 mg/d vs. placebo for 1 y as prophylaxis	Prevalence of depression did not differ between groups. No difference in stroke outcome or functional outcome was found.

[a] An antagonist at α_2-adrenergic pre- and postsynaptic receptors and 5-HT_2 receptors, similar to mirtazapine, available in Europe.
[b] A norepinephrine reuptake inhibitor available in Europe.
[c] A so-called cognitive enhancer used in patients with Alzheimer's disease.
[d] A Chinese herbal antidepressant.
[e] A depression rating scale.
CVA, cerebrovascular accident; FEWP, Free and Easy Wanderer Plus; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; PSD, poststroke depression; QOL, quality of life; SR, sustained release.

in reversing depression, reducing anxiety, and improving performance of daily activities [63]. Treatment with either antidepressant significantly increased the survival of depressed patients and, interestingly, nondepressed patients as well [80]. Other studies [64–67], although not all [68], found that fluoxetine was more effective than placebo for PSD. Citalopram [69,70], venlafaxine [71], and methylphenidate [72] also have been beneficial. Recently, Jorge et al. [81] found that poststroke patients who received escitalopram showed more improvement in global cognitive functioning than did patients who received placebo or problem-solving therapy. Moreover, this effect was independent of the antidepressant effect of the SSRI. Fluoxetine and sertraline may be more effective for emotional incontinence and anger proneness after stroke than for depression [68,73]. Nortriptyline [74], fluoxetine [74], escitalopram [75], and mirtazapine [76] were effective in preventing PSD; sertraline had mixed results [77,78], and mianserin was ineffective [79].

Electroconvulsive Therapy

ECT is a safe and effective treatment that may be used in cases of severe or delusional depression or when more conventional therapies cannot be used or are ineffective or intolerable to patients. Found to be particularly helpful in the depressive states accompanying stroke, Parkinson's disease, and dementia, ECT has become part of the standard of care for treatment of severe depression in the medically ill [82]. ECT is also used to treat catatonia.

There are no absolute contraindications to ECT, but patients with unstable cerebro- or cardiovascular disease or increased intracranial pressure warrant closer scrutiny [83–85]. The decision to proceed with ECT or not is made after a careful weighing of the risks of the treatment itself on any underlying physical morbidity against the risks of ongoing untreated depressive illness. This calculation is best done by a psychiatrist experienced in ECT in consultation with an anesthesiologist and other specialists. The latest research in this area has examined the memory impairment associated with ECT and the relationship of lead placement (e.g., bifrontal, bitemporal, and unilateral) to cognitive function [86–89].

Psychological Management

Although pharmacologic treatments are the mainstay of treatment for depression in the ICU, psychological remedies are also important. Patients often benefit from information, clarification, reassurance, and support. Psychological therapies are most useful in cases of adjustment disorder with depressed mood, often as an adjunct to pharmacologic interventions. Evidence has shown that brief psychotherapy at the bedside can give way to increased resilience and hope [90].

When patients come to the ICU, they are often terrified about the outcome of the illness that brings them there. They frequently believe that the illness, no matter how well controlled in the ICU, will continue to be life-threatening after discharge. Some patients believe that their illness will necessitate a radical change in lifestyle. For example, many cardiac patients secretly believe that having had an MI means they will never be able to have sex again. One way to help patients with such concerns is to ask specific questions about how they believe their illness will affect daily life in the future. In this way, one will hear the patient's specific fears and be able to educate the patient about the real effects of the illness. Another example is the patient who is physically weak after an MI and thinks he or she is a cardiac cripple. The patient does not understand that the physical debility is the result of muscle wasting from prolonged bed rest. Education often reassures patients.

Another way to help patients cope with depression in the ICU involves learning about a patient's premorbid activities. Because patients in the ICU feel stripped of their identities and are demoralized, showing interest in who they are and what is important to them can remind them that they are respected and have lives outside the hospital. Families also can be helped to have realistic expectations. Strategies to help patients and families cope effectively in the ICU are discussed in Chapter 201.

CONCLUSION

Treatment of depression in ICUs is multifaceted. Many difficulties are involved in treating depression. Nevertheless, aggressive treatment of depression in the ICU can drastically improve a patient's sense of well-being and transform a demoralized, hopeless patient into an active participant in treatment. In this chapter, we have outlined the recognition, differential diagnosis, and treatment of depression in ICUs. We strongly advocate that depression be treated as a serious illness; although a depressed mood is sometimes understandable, a depressive disorder is never appropriate.

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CHAPTER 200 ■ MANAGING THE SUICIDAL PATIENT IN THE INTENSIVE CARE UNIT

SAORI A. MURAKAMI AND HOA THI LAM

The assessment of the suicidal patient is a significant challenge for any intensive care team. Even when a psychiatrist is consulted to conduct an expert assessment of risk and to assist with the formulation of a treatment plan, the intensivist's ability to evaluate, manage, and safeguard the patient's safety is essential. The evaluation and management of a patient—whether contemplating suicide or recovering from a suicide attempt—require an understanding of risk factors, protective factors, the interplay among these various elements, and the relationship between staff and patient. In addition, the primary medical team should be aware of the necessity for ongoing psychiatric care during and after the stabilization of acute medical issues.

This chapter reviews the epidemiology of suicide, risk and protective factors, parasuicide, and intervention and

management strategies for suicidal patients in the intensive care unit (ICU).

EPIDEMIOLOGY OF SUICIDE

Suicide is the 11th leading cause of death in the United States (8th in men, 16th in women) [1]. In 2006, suicide was responsible for 33,300 deaths, with higher rates among whites, youths, and individuals more than 65 years of age [2]. Although no recent national estimates of the number of admissions to ICUs due to suicide attempts are available, in 2008, 376,306 people presented to an emergency department for treatment of self-harm, and 163,489 people were hospitalized due to self-inflicted injuries [1].

RISK AND PROTECTIVE FACTORS

Although appraisals of suicide risk are incapable of absolute predictions of suicidal behavior, careful history-taking, detailed examination, and astute clinical judgment allow a comprehensive understanding and evaluation of risk factors, protective factors, and the interplay among them (Table 200.1).

The first set of factors is sociodemographic, including age, gender, race, marital status, and religion. In general, men are more likely to complete suicide, whereas women are more likely to make attempts [1,3,4]. White men are more likely to attempt suicide than nonwhites; among nonwhite populations, rates vary [1,3]. Suicide rates increase in two particular age distributions: late adolescence to young adulthood and older than age 65 [1,2,5]. In general, the suicide rate is greatest among divorced and widowed people, followed by single individuals, and married people [5]. The combination of age, gender, and marital status also plays a role; young widowed men have a particularly high rate of suicide [5].

Some evidence suggests that religious beliefs and the strength of one's religious convictions protect against suicide; however, for some, religion may increase suicide risk. For example, an individual who believes he will be reunited with his lost loved ones when he himself dies may be comforted by the idea of dying. Thus, the various meanings religion can have in different people's lives mandate careful exploration with the patient of the role of religion in death and suicide [5,6].

Psychiatric illness contributes significantly to the risk for suicide. Retrospective studies have identified one or more psychiatric disorders in individuals who have completed suicide or presented following a suicide attempt [7,8]. In addition, conditions often comorbid with psychiatric illnesses (e.g., substance use disorders) increase the risk for suicide. The presence of a past history of suicide attempts, suicidal thinking, self-injurious behavior, impulsivity, assaultiveness, and trauma (physical or emotional) is an important component of risk assessment. Whether a patient is in active outpatient psychiatric treatment—and compliant with it—is also critical. Psychological factors—coping skills, tolerance of emotions, personality traits, insight, and judgment—figure prominently in the estimation of how a patient handles stress.

The presence of a physical illness contributes to the risk for suicide, with the number of physical illnesses increasing the risk for suicide in a linear fashion [9]. Suicide risk is greater in patients with neurologic disorders (e.g., Huntington's chorea, organic brain syndromes, multiple sclerosis, spinal cord injuries), and suicide attempts are more common in patients with epilepsy [5,10,11]. In addition, head trauma is associated with an enhanced risk for suicide, particularly when behavioral or cognitive sequelae result. Executive function deficits due to delirium, dementia, or mental retardation also contribute to the risk for suicide. Other illnesses of significance are listed in Table 200.1 [5,12].

TABLE 200.1

RISK AND PROTECTIVE FACTORS FOR SUICIDE

Sociodemographic factors
Age
Gender
Race
Marital status
Religion
Psychiatric history and present psychiatric conditions
Psychiatric disorders
Substance abuse/dependence
History of suicide attempts
History of self-injurious behavior
History of homicidal or assaultive behavior
Impulsivity
History of physical or emotional trauma
Psychiatric treatment, both outpatient and inpatient
History of treatment adherence
Psychological factors
Medical history and present medical conditions
Neurologic disorders
Head trauma, with or without cognitive and behavioral sequelae
Executive function deficits
Malignancies
Human immunodeficiency virus infection
Acquired immune deficiency syndrome
Peptic ulcer disease
Chronic inflammatory diseases
Hemodialysis-treated chronic renal failure
Heart disease
Chronic pulmonary disease
Family history
Psychiatric illness
Substance abuse/dependence
History of completed suicide
Psychosocial stressors
Family life
Work life
Relationships
Finances
Recent real or perceived loss

Adapted from American Psychiatric Association: Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. Arlington, VA, American Psychiatric Association, 2003. Available at: www.psych.org/psych_pract/treatg/pg/Practice%20Guidelines8904/SuicidalBehaviors.pdf. Accessed January 2, 2010.

Psychosocial stressors—including states of family life, work life, relationships, finances, and losses—are important considerations when assessing risk. A family history of psychiatric disturbances, substance use, or completed suicide may indicate potential genetic vulnerabilities in management of these stressors and response to interventions.

Protective factors include the presence of supports (e.g., family, friends, faith) and the absence of risk factors.

Risk and protective factors must be understood on a case-by-case basis [13–15]. Despite the significance of each factor, the weight to attribute to each element must be individualized, as the interaction among these features defines each patient's unique risk. For example, a 70-year-old unmarried white man with an incurable malignancy may be protected from suicide

by his religion's prohibition against it and by his three grandchildren's frequent visits.

PARASUICIDE

Some physicians may differentiate "genuine" suicide attempts (in which the person's aim was to kill himself) from parasuicide, a term introduced by Kreitman meaning "a non-fatal act in which the individual deliberately causes self-injury or ingests a substance in excess of any prescribed or generally recognized therapeutic dosage" [16]. Often, parasuicide is not a failed attempt to kill oneself per se, but could be either a maladaptive way to cope with emotions or an effort to elicit a specific reaction from someone else, whether an emotional response (e.g., feeling hurt or sorry) or a behavioral one (e.g., forestalling abandonment or providing nurturance). As such, a physician may be tempted to construe parasuicide as less concerning than an authentic attempt to end one's life. However, these individuals require equal attention and caution because parasuicide often recurs; when repeated often enough, such behavior may prove lethal, even if death is unintended. Furthermore, parasuicide may leave the person subsequently suicidal [17,18]. For example, a man who commits parasuicide in an attempt to keep his wife from divorcing him may feel genuinely suicidal if his wife ends up leaving him.

TREATMENT OF THE SUICIDAL PATIENT

Nonpharmacologic Interventions

A patient's verbalization of intent to harm himself or herself poses a unique challenge for the ICU physician. Although such utterances can be variously motivated and belie different intentions, any such statement should be taken seriously and viewed as the patient's request for help and support. Suicidal statements may take the form of explicit declaration or implicit action (e.g., refusal to eat or to cooperate with care). The suicidal act can be impulsive or deliberate. Because accurate prediction of which statements will result in action is impossible, the ICU team must institute effective precautions whenever a patient avows suicide.

The ICU team should implement close monitoring, in the form of constant observation by a one-to-one sitter or more frequent checks of the patient. Physical restraint of a patient at ongoing risk may be necessary when constant observation is not possible [12]. Staff should be aware of potential means by which patients may harm themselves. Any opportunity of jumping from windows or of hanging should be minimized, if not eliminated. All material that a person may use to harm himself or herself (e.g., razors, scissors, needles, glass, medications, and eating utensils) must be removed and any personal belongings searched for these items. Staff should also be aware of items brought in by visitors. The team should review medications and consider decreasing or discontinuing medications that may heighten impulsivity or disinhibition. Estimations of safety should be made at least daily.

The primary team must also identify and address among themselves any negative feelings they have about the patient. Emotional reactions to dealing with psychological problems in the ICU can include helplessness, insecurity, fear, anxiety, guilt, and sympathy. People who repeatedly attempt suicide or whose motives have been deemed "manipulative" can engender frustration, anger, and exhaustion with demands for constant attention, thereby creating distance between the patient and the treatment team. It is important to understand these feelings and to prevent them from hampering patient care and clouding recognition of a potentially unsafe patient. For example, patients with borderline personality disorder can "split" the staff (i.e., behave well for one subset of the staff and badly for another) [19]. Regular communication among staff members and between the staff and the patient can minimize splitting and prevent team members from feeling defensive or apologetic in the face of a critical and demanding patient.

An empathic approach that seeks to understand what the patient feels can prevent these emotions from instigating countertherapeutic responses. Even if a "suicide attempt" is an effort to elicit a particular response from others (rather than a genuine attempt to end one's life), the desperation required to put one's life at risk is nonetheless sobering. For people whose intent was to die, waking up from an unsuccessful suicide attempt can be accompanied by despair, shame, guilt, fear, anger, a sense of inferiority, and ambivalence about having survived [20]. The physical discomfort of the life-sustaining measures employed in the ICU only compounds such patients' pain.

Medications

The question of whether and when to restart psychiatric medications following a suicide attempt can be a difficult one, particularly if the person attempted to kill himself or herself by overdose on these agents. The decision to resume outpatient medicines must be guided first and foremost by accurate psychiatric diagnosis. They should not be restarted reflexively just because they had been prescribed previously; they should be ordered only if the patient has a bona fide psychiatric condition. Psychiatric consultation can be beneficial when the diagnosis is uncertain.

The next consideration is the patient's physical condition and the medications' effects on organs that the suicidal act may have compromised. Medications that are potentially toxic to impaired organs should not be restarted. Attention should also be paid to the patient's level of arousal and the risks for seizures and arrhythmias because psychiatric medications may enhance these risks.

Anxiety is a potent risk factor for suicide and should be treated to prevent recurrence of suicidal behavior and intensification of suicidal thinking. Benzodiazepines can be particularly helpful in quelling anxiety, whereas neuroleptic medications—both conventional and atypical—are preferred when anxiety escalates into outright fear. For full discussions of the use of neuroleptic agents and benzodiazepines in the ICU, see Chapters 197 and 198, respectively.

Psychiatric Consultation

Psychiatric consultation is strongly recommended whenever a patient's safety is questionable. The consultant will address psychiatric diagnosis, suicide risk, medications, and disposition. Consultation can also be helpful in understanding the psychological dynamics between patient and staff. The patient who may be thinking about, or at risk of, self-harm but has not articulated a specific thought may also benefit from expert consultation; elderly patients often do not report suicidal thoughts to caretakers [21,22].

When requesting a consultation, it is helpful to provide the consultant with as many details of the suicide attempt as possible (e.g., method, number of pills in cases of ingestion, likelihood of rescue). The exact words used by a patient who makes a suicidal comment, as well as the context in which the statement was made, are critically important and should be included in the consultation request. Basic elements of the patient's mental status (e.g., level of wakefulness, affect, presence of psychosis,

and ongoing suicidal thinking) should be determined and relayed to the psychiatrist.

Clear documentation from the nursing staff and physicians will help the consultant follow the patient's course and identify points of intervention. The existence of a suicide note can be of particular help in the assessment of suicide and in intervention planning [23]. However, whether to keep the suicide note in the permanent medical record is not clear. The suicide note can be of help to subsequent treaters; yet, in deference to the patient's privacy, a brief and general discussion of the note's existence and content may be all that is necessary for the medical record. The resolution of this matter should be made in consultation with the psychiatrist.

Disposition

When medically and surgically stable, patients face two options for discharge—home or psychiatric facility. Patients who may benefit from or require continued treatment in a psychiatric facility are those whose risk factors outweigh their protective factors. This decision is usually made with the psychiatric consultant, who will also assist with placement, prior authorization (which is required by some insurance plans), and the handling of any legal matters (e.g., if the patient is unwilling to be hospitalized psychiatrically and thus requires involuntary commitment).

CONCLUSION

Suicide is a tragic consequence of mental and physical illness that represents a relatively small number of ICU admissions. Nonetheless, the care of a patient who is suicidal or has just attempted suicide requires attention to a number of details not usually considered in the management of a typical ICU patient. The ICU team must be cognizant of their emotional reactions to the patient and of patient–staff dynamics, vigilant for potentially dangerous objects in the physical environment, and knowledgeable about specific interventions, including constant observation of the potentially self-harming patient. Psychiatric consultation can be helpful in managing important aspects of care for this patient population, from diagnosis and safety assessment to medication management and disposition.

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CHAPTER 201 ■ PROBLEMATIC BEHAVIORS OF PATIENTS, FAMILY, AND STAFF IN THE INTENSIVE CARE UNIT

CRAIGAN T. USHER

The ear says more
Than any tongue.

W.S. Graham, "The Hill of Intrusion"

Whether a patient being treated in the intensive care unit (ICU), a supportive family member, or a physician or other healthcare professional working there, it is clear that the ICU is a stressful environment [1–5]. Problematic communication among patients, their families, and the hospital staff can hinder the restoration and maintenance of basic life functions that are the hallmark of intensive care. Occasionally, such difficult patient–staff or family–staff interactions stem from problems with care providers themselves. Depression, anxiety, overwork, sleep deprivation, longstanding interpersonal rigidity, and the cumulative effects of stress may cause some physicians and nurses to fail to address adequately the emotional needs of their patients and patients' families [6–8]. In other instances, patients and families become overwhelmingly stressed, their judgment and interpersonal skills rent asunder by longing, shame, rage, and despair. Such patients and family members may then act in ways that are irritating or even dangerous.

This chapter presents approaches to problematic patient conduct in the ICU, details common patterns of exasperating behavior in critically ill patients, provides practical ways of dealing with them empathically, and outlines some effective modes of communication with families of patients in the ICU. Above all, this chapter emphasizes that listening to patients and family members, paying special attention to the psychological needs underlying problematic behavior, and attempting to meet those needs make better patient–doctor/family–doctor relationships possible.

APPROACH TO PROBLEMATIC BEHAVIORS

Critically ill patients can behave in disruptive ways that jeopardize ICU activity and treatments. Some patients become childlike, cry or whimper, turn away from care providers, and refuse examinations or procedures. A number of patients grow demanding of nurses' and physicians' attention; they hurl insults when providers are not as attentive as they would like. Others may be violent, threatening staff, even punching and kicking caretakers.

Before deciding how to approach the disruptive patient, one must first answer the questions "Do I feel safe?" and "Is the patient safe?" ICU personnel learn to override their fears as they perform procedures that demand brisk, decisive action. Unfortunately, such denial occasionally leads to failure to heed an internal alarm regarding patient behavior, resulting in injury to patients and staff. Hence, it is key to "tune-in" to this sense of peril when acute danger to a patient or others exists and then to administer calming medications, summon security personnel, and apply physical restraints if necessary [9]. Physical confrontation with a non-delirious patient can sometimes be avoided by calling security personnel expeditiously, as merely seeing several officers, patients recognize the seriousness with which staff is approaching their threats or actions—and then relax.

For example, emerging from delirium after a near-lethal toxic ingestion, an impetuous adolescent threatened to "beat up" staff if not permitted to leave the ICU immediately. When hospital security arrived and the physician informed the young patient he would have to wait, the teenager quickly sat back in bed. Asked by the psychiatric consultant why he had calmed, the young man explained: "When it was just the nurses and doctor, I thought I could take them. But I knew I wasn't going anywhere when the police arrived. So I chilled."

Once the safety of the patient, other patients, and staff is ensured, examination of underlying causes of a patient's taxing behavior follows. As irritability and emotional lability are the final common pathway of myriad medical and psychiatric conditions and of normal emotional responses, precise determination of the cause of a patient's disruptive behavior is often vexing. Asking and answering the questions listed in Table 201.1 can be helpful in narrowing the vast differential diagnosis.

Delirium is a common source of troublesome patient behavior in the ICU. Patients who are hallucinating or harboring persecutory delusions that ICU staff is torturing them can be immensely problematic. Due to its potentially lethal nature [10], delirium should be ruled out first as the driving force behind a patient's disruptiveness. A full discussion of delirium is provided in Chapter 197.

After delirium has been excluded, it is important to look for major psychiatric illnesses, which are frequently exacerbated by the chaos, vulnerability, and prolonged inner tension associated with being treated in the ICU [11]. The intensivist should discern if the patient has a history of psychotic disorder, affective illness, or anxiety disorder and, in the absence of contraindications, should order any medications that have been effective in treating these conditions in the past. As part of this psychiatric workup, a substance-use history is also imperative; data from collateral sources may be necessary to confirm the patient's report. At any step in the process of assessing the roots of patients' problematic behaviors, psychiatric consultation may be useful in establishing and confirming diagnoses and in guiding treatment.

While gathering data about psychiatric conditions and substance use, common sources of patient stress in the ICU (e.g., pain, sleeplessness, and isolation) should be eliminated, as much as possible. Biancofiore et al. showed that liver transplant recipients and patients who underwent major abdominal surgery identified "being unable to sleep, being in pain, having tubes in nose/mouth, missing husband/wife, and

TABLE 201.1

KEY QUESTIONS ABOUT BEHAVIORAL PROBLEMS IN THE INTENSIVE CARE UNIT

Safety
Is the patient's behavior dangerous? If so, how can I keep the patient and others safe?

Delirium
Is the patient delirious? If so, am I effectively treating the underlying causes of delirium?

Psychiatric illness
Does the patient have an anxiety, mood, or psychotic disorder or other psychiatric illness? If so, am I providing adequate treatment for these conditions?

Intoxication and withdrawal
Is the patient intoxicated with or withdrawing from alcohol or other substance? Am I addressing the untoward effects of withdrawal?

Psychosocial stressors
Can I reduce pain, sleeplessness, isolation, and other stressors related to being in the ICU?

Personality problems
What is the patient's predominant mode of coping? How can I best manage this patient's uniquely taxing coping strategies?

seeing family and friends only a few minutes a day as the major stressors" [12]. Provision of adequate analgesia, effective sleep aids, anxiolytic agents, and uninterrupted interaction with significant others often substantially curtails problematic behaviors.

COMMON PATTERNS OF PROBLEMATIC BEHAVIOR

Critical illness leads many patients to feel lonely, dependent, or anxious about the prospect of death; traumatic memories may be reawakened as well. To keep these unpleasurable feelings and recollections at bay, ICU patients deploy a broad array of psychological defenses. Some patients' patterns of defense—that is, their personalities—are quite adaptive, even at times of stress. Other patients are devoid of the healthy emotional protoplasm, reliable social supports, and ample psychological armamentarium required to deal well with adversity. Such patients may be said to suffer from *psychosocial insufficiency*. Through denial, devaluation, passive-aggressiveness, and other primitive defenses [13], these patients are prone to wreak havoc in the ICU.

Psychosocially insufficient patients fall into two categories: (a) those with personality disorders who were difficult to deal with even before becoming critically ill and (b) those who have simply regressed and use primitive coping mechanisms that, outside the ICU, would be less apparent. Because the focus in the ICU is on the "here and now," distinguishing between these two categories is unnecessary. More important is recognition of pathologic personality styles [14] that frequently engender loathing in ICU personnel and require limit-setting, validation, and a commitment on the part of the physician to have a different, less unpleasant type of relationship with the patient (Table 201.2).

The Dependent Patient

Dependent patients demand assistance in nearly every aspect of their ICU experience. Through urgent requests for

TABLE 201.2

COMMON PROBLEMATIC COPING STYLES OF PATIENTS AND FAMILY MEMBERS IN THE INTENSIVE CARE UNIT

Personality type	Core deficit	Characteristic behavior	Suggested response
Dependent	Hypersensitive to abandonment, inadequacy, and aloneness	Craves attention Demands special care Childlike Cries easily and complains of abandonment and inadequate care	Schedule examination and rounding times Anticipate nursing staff changes, physician care shifts, transfer to floor Validate patient's plight and offer to help within reason
Narcissistic	Hypersensitive to loss of control and stature Defended against looking weak	Denies severity of illness Shows bravado Critical of ICU staff and care	Acknowledge patient's stature Enlist patient as active partner in care and decision-making
Obsessive	Hyperaware of loss of control Defended against looking weak	Excessive focus on medical facts and minutiae Restricted affect Not apt to "show emotional cards"	Schedule patient and family meetings Have a set amount of information to share with patient and family Provide factual explanations of data Avoid emotional commentary or inquiry
Dramatic	Difficulty feeling cared for or thought of except within emotionally extreme exchanges	Engaging and charming to some staff, denigrating and caustic to others May have multiple allergies and phobias May "fire" some staff and take exception to rules	Acknowledge patient's positive attributes Validate patient's plight and offer to help within reason Set limits as a team

Adapted from Kahana RJ, Bibring GL: Personality types in medical management, in Zinberg NE (ed): *Psychiatry and Medical Practice in a General Hospital*. New York, International Universities Press, 1965, p 108.

spoon-feeding, bedpan assistance, pillow adjustment, analgesia, and better food, among sundry other entreaties, dependent patients drive nurses and house officers to distraction. Yet, when examined through a sympathetic lens, one finds that dependent patients are incredibly fearful and leverage demands for care to keep their nurses and doctors in sight, thus reducing their anxiety. In this way, demanding patients are like the infant who, unable to hold onto the mental image of his mother, wails when she leaves the room. These patients are hypersensitive to aloneness. To mitigate these fears, nurses and doctors should keep such patients informed (e.g., when they plan to return, when rounds will take place, and when family will visit).

Still, for many dependent patients, basic information of this sort is insufficient to quiet their incessant demands for instant anxiety reduction. In these situations, validation of these patients' feelings, communication that their requests are understood, and explanation that the staff is unable to provide everything these patients want are key. These tasks are often accomplished through "I wish" statements. For example, a particularly dependent and anxious patient in a busy ICU pled for her ICU team to stay in the room. Respecting that the patient felt she needed more security than she was experiencing, the team leader responded: "While I wish we could stay here longer to explore your questions and provide further reassurance, unfortunately we need to complete rounds. However, I will return at noon to check on you." By validating the patient's needs, acknowledging her personal limitations, and providing reassurance about the time of return, this physician better met the patient's dependency needs.

The Narcissistic Patient

Being critically ill in the ICU can lead the most psychologically healthy person to feel infantilized; hence, for most patients, regaining a sense of control is extremely important. For some patients, however, this need to regain control takes the form of entitled demands and scathing critique. These patients often admonish nurses ("You're not doing that the right way!"), belittle their doctors (e.g., calling young house staff "Doogie Howser"), and name-drop ("Dr. Smith is an expert cardiologist I play golf with, and he would never allow that").

With such patients, it is best to appeal to, rather than to confront, their narcissism. When the narcissistic patient looks around the ICU, all he sees are his inadequacy, inability, and incapacity. The intravenous pump reminds him he cannot feed himself, the ventilator brings to mind that he cannot breathe unaided, and the bedside commode or bedpan becomes a glaring reminder of his inability to move about nimbly. By using words that remind the patient that, despite his infirmities, he is still a valuable person, one then "joins" the patient and incurs less wrath and invective. Such "joining" can be done by respectfully calling patients "Mr.," "Ms.," and "Dr.," as appropriate. It is also helpful to ask them about their lives outside the hospital, promoting the notion that they are not frail and infantile but able-bodied adults endowed with personal agency despite their current debility.

The narcissistic patient, with his sense of specialness and need for excessive admiration, appreciates any control he can be afforded. Even if this means controlling the light switch, choosing the hour the physical therapist will arrive, or using patient-controlled analgesia, the narcissistic patient revels in being a partner in his care. Finally, avoidance of power struggles and sharing of dilemmas are key to working with these patients effectively. For example, an astute medical intern said to a "very important person" (VIP) in the ICU: "While I realize the catheter is completely uncomfortable, if I were to remove it right now, it is likely I would have to replace it tomorrow. I can do this if you'd like—it is your decision—but I am concerned that this would cause you even greater pain." Knowing he had a choice, the VIP felt greater self-agency and was thus able to defer to the doctor's educated opinion, electing to leave the catheter in for the time being.

The Obsessive Patient

The obsessive patient is rules-based and acts much like an early school-age child clinging to the rules of a board game. Following the obsessive mantra "a place for everything and everything in its place" [15], the obsessive patient wants to know what his radiograph shows before it is even taken. His day can rise and fall on laboratory minutiae. Like the narcissistic patient, the obsessive individual feels his control slipping away at times of illness. However, rather than acting in a haughty manner to deny that illness is stripping him of his control, the obsessive patient attempts to attain mastery over his condition through excessive focus on detail. A master of "losing the forest for the trees," the obsessive patient gets mired in the fine points. He asks questions incessantly and wants to manage his own treatment. For example, one obsessive patient with myasthenia gravis espied an "L" next to her hematocrit and demanded to know why she was not being transfused when her hematocrit was 32.3%. When her nurse sat down at her bedside and provided a synopsis of her laboratory results and the team's rationale for management, the patient was soothed. For all patients, but particularly for obsessive ones, it is helpful to: (a) have in mind a set amount of information that the team wants to share with the patient, thus allowing the patient the mastery over illness he or she craves but without overwhelming him or her; (b) announce a regular time when nurses and physicians will share a progress report; and (c) use scientific/deductive reasoning to explain each step in treatment.

The Dramatic Patient

With intense difficulty identifying their own affective state and the thoughts and feelings of others [16], extremely dramatic patients or family members, many of whom may suffer from borderline personality disorder, make erroneous assumptions about their caregivers' intentions. Based on little data, such patients sense that they are loved and appreciated by some, while loathed and apt to be mistreated or abandoned by others. The dramatic patient or family member thus idealizes and praises some staff members while alienating others with toxic devaluation and belligerence. Even the most mindful, well-meaning, intelligent physician or nurse can find himself or herself suddenly on the wrong side of this idealization/devaluation "split." Validating patients' feelings but not necessarily their beliefs can be helpful. For example, one family member berated a physician: "You must hate our family!" The physician responded: "I am surprised to hear you say that, because I am not aware of having bad feelings toward you or your family. I wonder what gives you that impression." The family member then explained that the doctor seemed to turn away from the family when he passed by the visitors' lounge and "did not do nearly enough family meetings." Now understanding that this person required more information and dialogue than he customarily provided, the physician agreed to have more frequent meetings and made a concerted effort to acknowledge the family's presence when passing them, and thus enjoyed a more positive working relationship with this family member.

When clinicians who have had completely different experiences with a dramatic patient or family member confer, they are at odds over how to handle the dramatic individual's demands. This discord creates tremendous tension among treatment team members and can be relieved when clinicians acknowledge they

TABLE 201.3

PRINCIPLES OF ESTABLISHING LIMITS AND NEGOTIATING CONFLICTS IN THE INTENSIVE CARE UNIT

Acknowledge the patient's real struggles.

Explain limits in a clear and concise manner. Avoid jargon such as, "You are demonstrating unsafe behavior, sir. This is a nonsmoking environment," and simply offer, "You can't smoke while you're in the unit."

Before speaking with the patient, know what areas, if any, are flexible and make concessions to the patient in those areas.

Determine consequences for transgressing limits in advance.

Avoid long, drawn-out arguments as they are rarely, if ever, useful. Leaving the patient's bedside to cool down, thinking of a new strategy, or consulting a colleague is better than acting impulsively.

Adapted from Winnick JA, Wool CA, Geringer ES, et al: Problematic behavior of patients, family, and staff in the intensive care unit, in Irwin RS, Rippe JM (eds): *Irwin and Rippe's Intensive Care Medicine*. 5th ed. Philadelphia, Lippincott Williams & Wilkins, 2003, p 2192.

have had divergent emotional experiences with a patient. Once this "split" is named, the team can then strategize how best to set limits (Table 201.3).

COMMUNICATION WITH FAMILIES

Almost always for better, but occasionally for worse, family members are not mere visitors to the ICU [17]. Families play an integral role in encouraging and comforting critically ill patients and informing distant loved ones of patients' progress or problems. With the exception of those patients who, prior to hospitalization, expressed their preferences for medical care, relatives are also responsible for learning about a patient's diagnosis and prognosis and making decisions for critically ill patients who lack the capacity to make medical choices for themselves.

It can be difficult to function in these roles, as the experience of having a family member in the ICU takes a psychological toll. One study revealed that 69% of family members of intensive care patients suffered depressive symptoms and 35% had anxious symptoms [2]. Azoulay and colleagues reported that up to one third of family members suffered posttraumatic stress symptoms 3 months after their family member was discharged from the ICU [3].

Adequate communication between ICU staff and patients' family members is central to reducing family stress and dissatisfaction [18,19], decreasing conflict around end-of-life decisions [20], limiting futile interventions [21], and reducing strife between families and ICU staff [22]. Some general principles of communication with families in the ICU include providing clear and concise medical information, scheduling and keeping appointment times to meet with families, respecting the uniqueness of the family and the patient, attending to special aspects of the patient's and family's life story, and providing early diagnostic and prognostic information, even if this means saying, "I'm not sure" [23,24] (Table 201.4).

Even with good communication, problems arise. Occasionally, before the physician can provide information regarding prognosis, family members will foreclose discussion and disagree with the doctor or other family members about how much workup or end-of-life treatment to pursue. Some special situations related to the emotional life of family members bear examination in further detail. These include the guilty family member, the family member compelled to preserve the dignity or "fighter status" of the patient, and the vindictive family member. Physician interventions or "conversational reframes" in these situations are aimed not at coercion but at enhancement of doctor–family and family–family conversation about how best to proceed with a critically ill family member's care.

TABLE 201.4

CORE PRINCIPLES OF COMMUNICATION WITH FAMILIES IN THE INTENSIVE CARE UNIT

*C*lear
Provide family members with clear, concise descriptions of the patient's condition. Avoid jargon. Ask if you have adequately addressed the family's questions and concerns.

*O*n time
Schedule appointments for family conferences or treatment updates and try, as best as possible, to be on time. Send a representative if you must.

*R*espect the patient's uniqueness
These appointments are as much about what you say as how well you listen. Pay close attention to people's names and what makes the patient special.

*E*arly diagnosis and prognosis
Even if it means saying, "I'm not sure," try to inform the family early in the ICU stay.

Occasionally, a sibling, parent, or child of an ICU patient who has played little role in the ailing family member's life attempts to rectify this estrangement by coming to the rescue at the 11th hour. To assuage their guilt, these family members demand that "everything" be done for their relative, to the point of pushing for futile assessments and treatments. Reframing the dilemma for these family members, giving them a sense of authority, and explaining how they can be helpful can shift the family–staff dialogue. For example, one intensivist told a particularly guilt-ridden son whose mother had suffered a severe stroke: "I know you've had to be away for several years and not been able to play a day-to-day role in your mother's care. However, this is a really big opportunity to help support your dying mother and your struggling sister. You can help your sister and the rest of your family come to a well thought-out decision about your mother's care." By suggesting how this young man could help in the here and now and indirectly addressing his guilt, the physician altered this concerned son's attitude.

When dealing with end-of-life care, some family members will demand that everything be done because they do not want their loved one to seem weak. "But he's a fighter," some relatives protest. In these situations, one should listen closely to why it is important that the patient's status as a "fighter" be maintained. Once this information is obtained, the ICU staff member might illustrate how the patient remains a fighter even as heroic measures are scaled back. For example, a 78-year-old World War II naval veteran was admitted to the ICU with a massive myocardial infarction from which a meaningful recovery was extremely unlikely. The patient's daughter touted the fact that her father had made it through polio, the Pacific campaign, and a kidney transplant, and refused even to discuss withdrawing ventilator support. Wed to the picture of her father as a warrior, this loving daughter asserted, "He's made it this far and he'll keep fighting." When the intensivist told the daughter he understood her father had made it through these

trying illnesses and battles, detailed the extent of her father's myocardial damage, and emphasized that it took a "remarkably massive" heart attack to bring him down, the daughter's vision of her father as a "fighter till the end" was affirmed. She was then more amenable to discussing end-of-life care and relaxed her terse "do everything" commands.

Some family members may be angry with the patient. Wasserman studied responses provided by relatives of patients who had attempted suicide and found that a family's request for "do not resuscitate" orders sometimes reflected anger toward the patient [25]. Eliciting these feelings during a family meeting may help family members to acknowledge the hostile origins of their decisions and to feel they have acted less impulsively and more thoughtfully about how to proceed with a loved one's care.

Communication between ICU staff and a patient's family may be disrupted when a family member does not want to make decisions on behalf of a loved one or suffers symptoms of anxiety, depression, or other psychiatric illness [26]. Such family members may derive great benefit from consultation with the ICU's social worker or an outpatient psychiatrist. When discussions over care reach a standstill and interventions spur little movement, referral to an ethics consultant or committee (particularly with regard to end-of-life care) or patient-rights advocate (regarding a family member's grievance) may help resolve the conflict.

CONCLUSION

Physicians, nurses, and other members of the critical care team are often confronted with patients and families whom they find taxing or even dangerous. Establishment of safety, exclusion of causes of disruptive behavior amenable to medical intervention, examination of the patient's and family member's predominant defense mechanisms, and attempts to address the patient's or family member's psychological needs better can improve such difficult interactions. Patients with personality problems often respond to validation of their distress and to limit-setting, entailing a description of how they are expected to act and what they can expect from their caregivers. Family members and loved ones play a crucial role in critical care; ensuring that they are part of the ICU team involves providing clear diagnostic information early on, conveying respect for the uniqueness of patients and their families, and providing regular, scheduled updates.

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CHAPTER 202 ■ RECOGNITION AND MANAGEMENT OF STAFF STRESS IN THE INTENSIVE CARE UNIT

GUY MAYTAL

Intensive-care settings reveal humanity at its best and at its worst. This is as true for the staff as it is for the patients. We who serve in intensive care settings in a true sense risk our own lives in these settings—our feelings, our self-esteem, our self-respect. By risking these daily we grow; by avoiding the risk we must face the dehumanization of ourselves or of our patients.

Cassem and Hackett [1]

The intensive care unit (ICU) is a structurally, functionally, and socially complex entity with its own culture, personnel, protocols, and problems [2,3]. Today, such units are routinely filled to capacity with complicated patients suffering from multiple life-threatening illnesses. As technology has advanced, patients with once-terminal illnesses are surviving longer, raising ever more complicated ethical issues [4].

For patients and their families, time spent in an ICU can lead to physical and psychological trauma [5–7]. The overall "hostile" environment of the ICU—with its multiple, complicated devices, lack of patient comforts, lack of privacy, and elevated ambient noise—contributes to negative psychological outcomes for patients [8].

This same environment also affects ICU staff. The psychological pressures on ICU personnel are myriad: increasingly sophisticated technological advances, overwhelming amounts of data, burdensome demands on caretakers, long hours, nursing shortages, and trying ethical issues. Staff may not be prepared to handle their emotional reactions to these challenges while simultaneously tending to the technical and clinical aspects of intensive care.

This chapter reviews the general concepts of stress and burnout, the tensions associated with training and working as a physician or a nurse in an intensive care setting, and strategies for managing staff stress in the ICU.

STRESS

The physiologic, cognitive, and affective facets of stress are based on the seminal early work of Selye [9] on the *general adaptation syndrome*. Selye defined stress as the nonspecific result of any demand on the body, and observed that different organisms and biological systems respond to stress in a stereotyped and predictable three-part pattern. The initial alarm reaction (characterized by activation of the sympathetic nervous system and various hormonal, immunologic, and psychological responses) is followed by the stage of resistance, during which the organism establishes a temporary homeostasis by marshalling various reserves to adapt to the new situation. However, the body's ability to adapt is finite, and, with continued exposure to the stressor, its reserves become depleted and the organism enters a stage of exhaustion.

Researchers in biology and sociology have expanded this work to encompass processes ranging from individual cellular responses to stress, to the reactions of individuals and social systems to external and internal stressors. The study of occupational stress (i.e., stress due to one's work situation) has grown substantially since the 1960s, expanding to professions ranging from factory work to nursing. Research during the past four decades has consistently demonstrated the significant adverse impact of excessive occupational stress on physical health, mental health, and decision-making. Regardless of the field, low job satisfaction is often predicted by a small number of factors: little participation in decision-making, ambiguity about job security, poor use of skills, and lack of clarity about role. These stressors are consistent with the *demand–control model* of the effects of job demands on worker's well-being. This model predicts that the fewer demands and more control a worker has on the job, the less stress he will experience [10,11]. For example, an analysis from the Swedish National Registry of 958,000 people found that hospitalization rates for myocardial infarction (MI) were higher among men and women with high-demand, low-control jobs [11].

Other well-recognized occupational stressors include noise-related stress, dangerousness of the work environment, nonstandard work hours, and excessive fatigue [10]. Of these stressors, work overload and a poor social environment at work are the most significant determinants of work-related health problems. Cross-sectional associations between work overload and health complaints are consistently reported [12,13]. Furthermore, work overload and overall low job satisfaction are strongly associated with the development of psychiatric (particularly affective) problems. A meta-analysis of job satisfaction and health outcomes examined 485 studies (267,995 individuals) and concluded that poor job satisfaction was strongly associated with the development of depressive and other affective illnesses [14].

In addition to physical and mental health, decision making also can be adversely affected by high levels of stress. Awareness of one's limited knowledge and problem-solving capabilities, fear that bad outcomes will occur regardless of which choice is made, worry about making a fool of oneself, and fear of loss of self-esteem if the decision is wrong can force decision-makers to come to "premature closure." Fearing a negative assessment of their sense of helplessness, otherwise rational decision-makers foreclose the decisional dilemma before a search for, and an unbiased assimilation of, all relevant information and generation and careful appraisal of all alternatives can be completed [15].

Such premature closure can lead to incorrect or even harmful decisions [15]. For example, in their classic study of patients with acute MI, Hackett and Cassem [16] noted that the majority of patients experiencing what they thought might be an MI delayed calling for help for 4 to 5 hours. In an effort to avoid

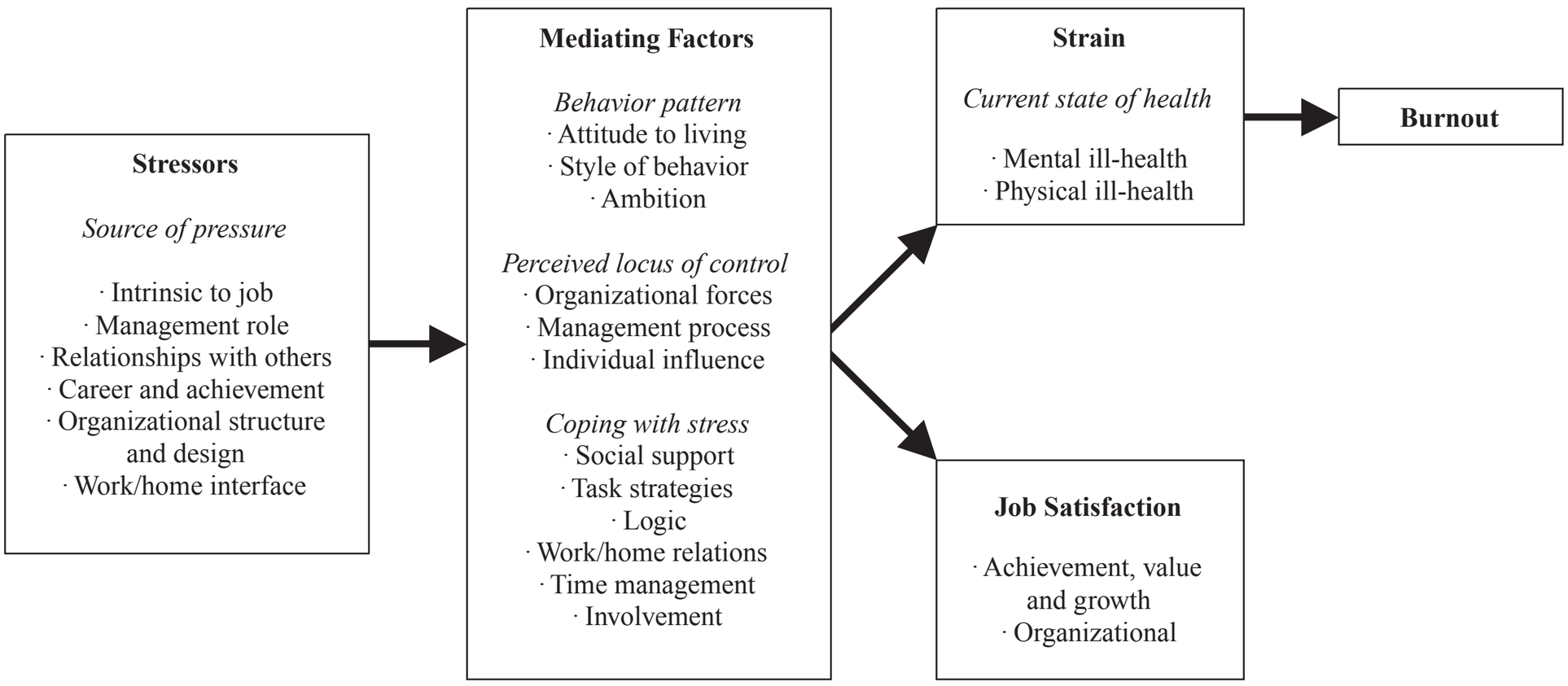

FIGURE 202.1. Stress–strain model of occupational stress. [Adapted from Cooper CL, Sloan SJ, Williams S: *Occupational Stress Indicator: Management Guide*. Windsor, UK, NFER-Nelson, 1988.]

the anxiety of a potentially devastating diagnosis and its implications, these patients came to premature closure and made potentially deleterious decisions about when to seek medical attention [17].

In a work environment, including the ICU, stressors (both work- and nonwork-related, both internal and external) affect each individual in a unique manner as mediated by a variety of factors. The interaction between stressors and mediating factors leads the individual to experience either strain or job satisfaction (Fig. 202.1) [18]. When this interaction leads to strain that is chronic or particularly intense (or both), burnout occurs.

BURNOUT SYNDROME

Coined by the clinical psychologist Herbert Freudenberger [19] in 1974, *burnout syndrome* has been viewed as a behavioral or a psychological condition as well as a process or a syndrome [20]. Research during the past 2 decades (especially by Maslach and colleagues) has narrowed the current definition to encompass the spheres of emotional exhaustion, depersonalization (i.e., negative or cynical attitudes regarding work), and the absence of personal accomplishment—particularly among individuals who do "people work" (Table 202.1) [21]. While emotional exhaustion is the key component of the syndrome, people with all three symptoms experience the greatest degree of burnout [22]. Ultimately, this definition describes a process whereby highly motivated and committed individuals lose their spirit, their motivation for creativity, and, in the ICU, their belief in their ability to help people [23,24].

Burnout varies in intensity and duration, although it often has an insidious onset [25]. Even if an individual's experience of burnout does not reach consciousness initially, it may affect others, burdening the system with another source of stress.

Many have argued that the cause of burnout lies in our need to believe that our lives are meaningful and that what we do is useful and important [23]. Work takes on a central role in providing some people with this sense of meaning in their lives. When individuals who derive such meaning from work think they have failed in their jobs, they may experience burnout. Burnout tends to afflict people who enter their professions with high motivation and idealism; it is particularly common in occupations often seen as "callings" [26]. In a supportive environment, highly motivated individuals reach their goals and achieve success, which leads to a sense of meaningfulness that itself increases the original motivation. However, in an unsupportive environment, these individuals cannot accomplish what they set out to do and consequently fail. For people who expect a sense of meaningfulness from work, such failure often leads to burnout.

Everyone experiences stress, but only those who start their careers with high levels of idealism, motivation, and commitment are at risk for burning out: "You cannot burn out unless you were 'on fire' initially" [23]. Burnout occurs almost exclusively in individuals who work with people, arising from the emotional stress that such interactions engender. ICU staff tend to be idealistic, committed, and driven—the very attributes which render them susceptible to burnout. In assessing and managing burnout, attention should be paid to the impact of job-related stressors and their ramifications, as well as the individual's personality style. The character trait of hardiness (i.e., initiative, willingness to take risks, ability to face uncertainty,

TABLE 202.1
THREE COMPONENTS OF BURNOUT

Emotional exhaustion	Reduced energy and job enthusiasm Emotional and cognitive distancing from the job
Depersonalization	Cynicism Lack of engagement and distancing from patients Treatment of patients as inanimate, unfeeling objects
Absence of personal accomplishment	A significantly diminished sense of efficacy, effectiveness, involvement, commitment, engagement, and capacity to innovate, change, and improve

Adapted from McManus IC, Keeling A, Paice E: Stress, burnout and doctors' attitudes to work are determined by personality and learning style: a twelve year longitudinal study of UK medical graduates. *BMC Med* 2:29, 2004.

and assertiveness in attaining and manipulating external rewards) has been shown to protect healthcare professionals (particularly nurses) from burnout in multiple stressful settings [27].

For the individual, burnout is characterized by physical, emotional, and attitudinal symptoms. Physical symptoms are nonspecific and include chronic fatigue, headaches, insomnia, weight changes, and worsening of chronic medical conditions. Burnout can lead to increased consumption of tobacco, alcohol, and illicit drugs. Emotional symptoms include despair, hopelessness, and depression. Relationships can become disrupted and the ability to work can be compromised [21].

On an organizational level, cynical attitudes toward work, colleagues, and patients can isolate coworkers and precipitate staff conflicts. At some hospitals, job dissatisfaction and burnout have led to absenteeism, accelerated staff turnover, and severe staff shortages, which may limit the number of ICU beds available for patient admissions [28].

STRESS AND BURNOUT IN HEALTHCARE PROFESSIONALS

Stress is a common aspect of medical practice for physicians, nurses, and trainees. Not surprisingly, studies over the past several decades have reported a high prevalence rate of burnout in healthcare professionals. Rates of burnout among physicians range from 25% to 60%, depending on working conditions and medical specialty [29–34]; burnout can develop at any stage of a physician's career. Nurses also experience high levels of burnout. Studies in nurses indicate rates of 35% to 50%, depending on working conditions, clinical setting, and level of autonomy experienced [22]. Multiple factors have been associated with burnout in healthcare professionals, but the best characterized include: heavy workload, stressful work environments (e.g., ICUs), severity of patients' illnesses, and conflicts with coworkers or patients [35,36].

Physicians who experience burnout suffer physical (e.g., anorexia, insomnia, tachycardia, and hypertension) and psychological (e.g., irritability, frustration, apathy, indecision, and depression) symptoms. Burnout leads to increased nurse distress, decreased patient satisfaction, increased mortality in the ICU, and substance abuse [37,38]. Furthermore, approximately 10% of physicians develop a substance-related disorder in their lifetimes; the risk of narcotic abuse in physicians is ten times that of the general population. Substance abuse often leads to sanctions and to loss of license and livelihood [39]. The primary risk factors for addiction in physicians include high stress levels, access to drugs, and chronic fatigue, all pronounced in ICU settings. Often shielded by a "code of silence" among fellow practitioners, impaired physicians often come to clinical attention in an advanced stage of addiction.

Just as concerning are the statistics on physician suicide. Male physicians are two times more likely to commit suicide than average Americans; female physicians are three times as likely [40]. Furthermore, physicians' personal relationships with spouses and children are damaged by burnout: "Being a physician is one of the few socially acceptable reasons for abandoning a family" [41].

STRESS AND ITS CONSEQUENCES IN PHYSICIAN TRAINING

During the past 20 years, the medical and sociological literatures have documented the impact that work-related stress has on physicians and on their ability to care for patients. Consequently, efforts have been made to understand the nature of stress and burnout in house officers, fellows, and staff physicians—particularly those who work in intensive care settings. Stress and burnout have been associated with deterioration of the physician–patient relationship and a diminution in both the quantity and the quality of care [37]. Therefore, burgeoning efforts have been directed to prevent stress and impairment and to improve the care of physicians suffering from stress or burnout [42–44].

Competitive, highly driven, and able to delay short-term gratification indefinitely, people attracted to medicine are more likely to have personalities that render them susceptible to the detrimental effects of stress and to burnout. As a rule, they are success-driven, tend to be "people-pleasers," and are unable to recognize their own limitations. Similarly, they do not often understand or attend to their own emotional and psychological health and, citing the need to be "strong," squelch their emotional reactions to stressful events [44].

Medical practice has changed dramatically over the past several decades, and many physicians who entered medicine to enhance their sense of control and mastery find themselves in a medical system that is increasingly out of their control [44]. Physicians have experienced a decline in status and autonomy alongside increased work pressures. Under closer scrutiny by regulatory agencies and insurance companies, physicians have had to contend with ever growing amounts of paperwork. Due to increased pressure to discharge patients, the acuity of patients in hospital settings has increased, "turnover" is more rapid, and interventions are more aggressive.

House officers, in particular, face a unique constellation of stressors. According to a review of the stresses of residency by Colford and McPhee [42], the stressors faced by house officers are varied, including those related to the nature and educational structure of residency, being a female resident, and perceptions about work. Among the most potent stressors are sleep deprivation, information overload, long work hours, and confrontation with chronic and fatal diseases. Others include financial debt (including from educational loans), personal relationships, and anxiety about malpractice. These researchers also found that alcohol and drug abuse was a significant problem in 7% to 10% of physicians. They cited studies verifying high levels of stress due to physicians' relationships, psychological problems (e.g., anxiety and depression), and professional dissatisfaction.

In recent years, more quantitative evaluations of the effects of stress and burnout on house officers have implicated residency-related stressors in contributing to psychiatric and physical impairment. Such stressors include overnight call, responsibility for four or five times as many patients at night as during daytime hours, lack of supervision while on call, the inability to complete a task without interruptions, and lack of substantive patient interactions [45–47].

In a longitudinal study that examined the impact of job stress on house officers, Tyssen and colleagues [45] followed 371 medical students from their last semester through the end of their internship. They found that 11% of these interns had mental health problems. Predictors of mental health problems included prior mental health problems, a high level of neuroticism, and experience of a serious negative life event during internship. Most important among these factors was perceived job stress. Furthermore, perceiving oneself as deficient in clinical skills or knowledge at the end of medical school was related to a mental health problem during internship. Importantly, gender, number of hours worked weekly, and lack of sleep were not linked to mental health problems.

In a similar study, Newbury-Birch and Kamali [46] examined the relationship among work-related stress, job satisfaction, and personality factors in 109 medical house officers. They found that 24% of the men and 38% of the women suffered from psychological stress. Levels of depression and

anxiety were significant among these house officers. The personality characteristic of neuroticism was a predisposing factor for stress and anxiety.

Shanafelt and colleagues [47] examined the relationship between burnout and self-reported patient care practices in a university-based internal medicine residency program. They found that 87 (76%) of the residents surveyed met criteria for burnout. Those residents who were burned out were much more likely to be depressed, have low career satisfaction, and report significantly more "suboptimal patient practices."

Stress and burnout are associated not only with work hours but with a variety of internal and external factors; quality of teamwork, personality characteristics, and trouble with the work/home interface all contribute to the development of stress and burnout in house officers. A 12-year longitudinal study of medical school graduates found that specific personality traits (e.g., high neuroticism, low extraversion, and low conscientiousness) measured while in medical school strongly predicted the development of stress, burnout, and job satisfaction as a staff physician [48].

Despite work-hour restrictions, house officers and fellows continue to shoulder stressful workloads that have a significant impact on their physiology and psychology [46]. Gopal and coworkers [48] studied a single cohort of residents before (2003) and after (2004) restrictions on work hours were implemented. Residents in 2004 had less burnout, emotional exhaustion, sleep deprivation, and depression. However, the residents did not perceive any significant changes in their quality of life, and their learner satisfaction was significantly reduced.

Parshuram and colleagues [49] prospectively studied 11 critical care fellows in Toronto, Canada, working within the Ontario guidelines limiting work hours and overnight call shifts. The researchers thoroughly examined the amount of work performed by the fellows (e.g., number of hours, admissions, procedures, pages). They also used Holter monitors to screen for arrhythmias, pedometers to measure distance walked, and urinalysis to evaluate hydration. The results showed that, despite work-hour restrictions, the fellows continued to work long shifts, with little sleep (average, 1.9 hours per night), frequent pages (average, 41 per shift), many admissions, and many procedures. Furthermore, they walked an average of 6.3 km per shift. More alarming was that abnormalities in heart rate and rhythm occurred in all participants. Ketonuria was found in 21% of the shifts during which it was measured, indicating dehydration and suggesting self-neglect.

STRESS AND BURNOUT AMONG INTENSIVISTS

Stress and burnout are not limited to house officers and fellows. Staff physicians—in particular those who work in ICUs—have a high prevalence of burnout syndrome. The protracted stress of working as a physician can lead to lower-quality patient care, disruptions in personal relationships, and even impairment of physical health [50]. Intensivists labor in an atmosphere of perpetual stress and often limited rewards. In addition, society often has unrealistic expectations of the physician not only as a professional but also as a spouse, parent, employer, and community member. Failure to live up to any of these can lead to a sense of failure [50]. A 2001 survey by the Canadian Medical Association found a significant decline in physician morale, due to volume of work, sleep deprivation, teaching and research demands, potential for litigation, and greater demands from the public [44].

In recent years, researchers have attempted to better quantify the way in which these stressors affect physicians who work in intensive care settings. Coomber and coworkers [38] surveyed all members of the Intensive Care Society in the United Kingdom (85% response rate, 758 respondents) to identify "distressed" doctors and to relate this state to "repeated and long-term exposure to job stressors." They found that nearly 30% of the physicians surveyed were distressed, 12% were depressed, and 3% had suicidal thoughts. These physicians reported that the most stressful aspects of their work were the feeling of being overstretched, the effect of work hours and stress on personal/family life, and the pressure to compromise standards when resources were limited. Other important stressors included perceiving a lack of peer recognition, feeling alone in making important decisions, and occasionally having too much responsibility.

In a recent survey of 978 French intensivists, Embriaco and colleagues [35] found that 46.5% had a high level of burnout syndrome. Risk factors included female sex, increased workload, and conflicts with coworkers. Similarly, in a survey of 6000 American physicians, female physicians were 60% more likely to report burnout than their male counterparts [51]. Furthermore, in the Embriaco study, workload (as measured by number of shifts per month and length of time from the last day off) was associated with higher rates of burnout. Lastly, conflicts with coworkers are associated with higher levels of burnout, while good relationships with nurses are a protective factor [35,36,52].

Given the high frequency of burnout in physician populations, the Academy of Professors of Medicine analyzed survey data from more than 4,000 physicians in the United States and the Netherlands and formulated a model to predict burnout. Their model (Fig. 202.2) lists factors specific to physicians that place them at risk for developing burnout, and suggests areas of intervention to help prevent the development of this burdensome and costly syndrome [37].

STRESS AND BURNOUT AMONG INTENSIVE CARE UNIT NURSES

Although nurses and physicians work in the same physical environment, nurses have unique working conditions, emphasize

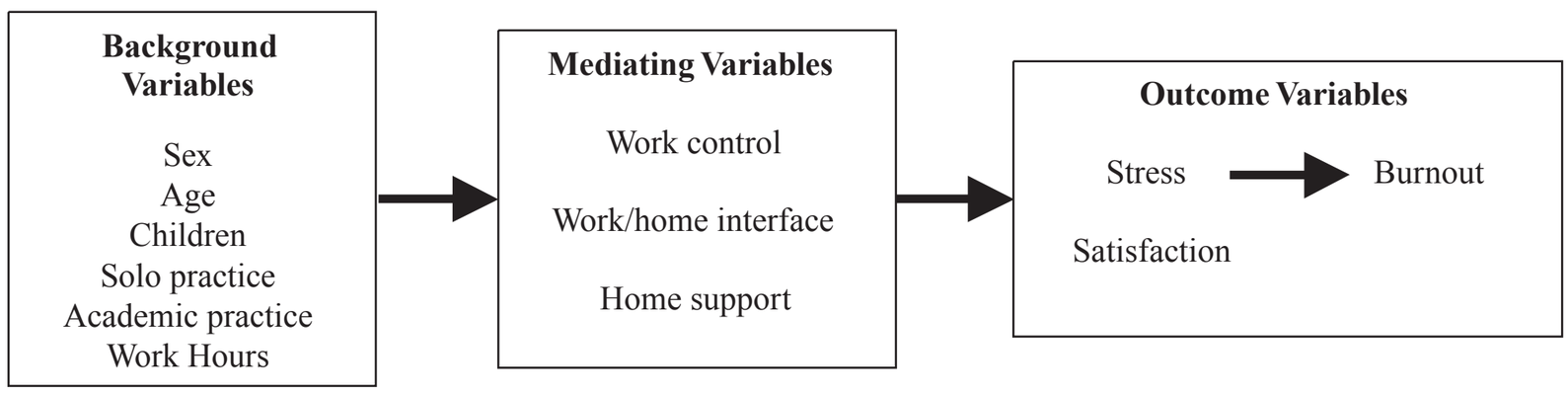

FIGURE 202.2. Model for predicting physician burnout. *Arrows* indicate a direct effect. [Adapted from Linzer M, Visser MR, Oort FJ, et al: Predicting and preventing physician burnout: results from the United States and the Netherlands. *Am J Med* 111:170, 2001.]

different aspects of clinical care, and experience different stresses. As one nurse stated in a study on burnout: "There is a mutual goal in your work as a nurse, no matter where you work, and that is to take care of the patient. Nursing is a job in which you are always under pressure. You are dealing with life and death issues on a daily basis. You can't come to work and say: I slept only five hours tonight and I'm tired. You have to be on full alert at all times. You work under incredible pressure with little rewards" [53].

Nurses usually work in the ICU indefinitely, compared to residents, and even critical care fellows and attendings, who rotate through different units in the hospital. Despite their relative permanence in the ICU, nurses do not generally accrue as much autonomy and stature as do physicians, which may lead to stress over career and organizational structure [54]. Poncet and colleagues [36] surveyed 2,392 French nurses working in 165 ICUs (mean time from graduation was 40 months and mean time working in the ICU was 36 months). Severe burnout was identified in 33% of the nurses surveyed. Four characteristics were independently associated with this outcome: younger age, organizational factors (e.g., less autonomy in scheduling days off), poor quality of working relationships, and factors related to end-of-life decisions. Other studies also have demonstrated that concerns surrounding ethical decisions are consistently the most important issues of ICU nurses [55]. In situations in which nurses attempt to reconcile their ideals regarding ethical dilemmas with the reality of their limited autonomy, stress can develop. Nurses with fewer workplace restrictions and thus greater autonomy have less anxiety and are more likely to advocate for their patients [56].

The personality trait of hardiness also can protect against stress and burnout among ICU nurses [57–59]. Aiming not merely at survival in the face of difficult circumstances but at the enrichment of life, hardiness consists of the triad of commitment (a sense of purpose expressed by becoming an active rather than a passive participant in life), control (the tendency to behave in a way that influences life events rather than to feel impotent in the face of adversity), and challenge (the belief that change, instead of stability, is normal and a stimulus to enhance maturity rather than a threat to security) [60]. Wright and colleagues [61] found a strong inverse relationship between hardiness and burnout in 31 intensive care nurses. Any interventions to reduce stress and burnout among nurses should include efforts to augment hardiness [62].

MANAGEMENT OF STAFF STRESS AND BURNOUT IN THE INTENSIVE CARE UNIT

Stress and burnout are common and deleterious to the ICU team. Therefore, preventing and ameliorating burnout syndrome in the ICU should be a priority. Ample descriptive reports of interventions to address stress and burnout in the ICU exist, but there are few outcome studies. Their general aim is to reduce stressors for staff, employing individual, interpersonal, and organizational strategies. The use of humor, support groups, and a system for outside referral are important in preventing and managing stress [45].

Individual strategies proposed to prevent burnout include relaxation training, time management, assertiveness training, team building, and meditation [21]. The aim of all such strategies is to enhance individuals' capacity to cope with the demands of their jobs [49,63]. For example, Isaksson Rø and colleagues studied the effectiveness of a 1-day individual session or a 1-week group intervention aimed to prevent burnout in 227 Norwegian physicians. They found that participants in either intervention had a significantly reduced level of emotional exhaustion as compared to physicians who did not participate [64].

Given that interpersonal conflict is a risk factor for severe burnout, improving the quality of relationships among doctors and nurses protects against burnout [35,36]. Groups and workshops have been reported as useful in managing stress [1,62,65,66]. Cassem and Hackett [1] described weekly and impromptu group meetings to explore ICU staff reactions to crises, to resolve conflict, and to discuss feelings, experiences, and knowledge. McCue and Sachs [62] described the effectiveness of a stress management workshop for medical and pediatric residents; it cost little, was positively received, and demonstrated significant short-term improvement in stress and burnout scores.

On the organizational level, reducing work hours and improving work organization is a first step toward burnout prevention [49]. Furthermore, ensuring adequate staffing, shared decision-making, active review of unit policies and procedures, freeing up time for patient care or research, bolstering administrative support, and allowing flexibility to curtail work/home conflict may help reduce stress and increase job satisfaction [37,67].

CONCLUSION

Recognizing and attending to staff stress in the ICU are necessary to ensure the continued effectiveness and well-being of each individual and of the unit as a whole. Left unaddressed, staff stress and burnout can exact a heavy price. As Civetta [68] wrote:

> We must accentuate the positive qualities of human capabilities that are beyond technological advancement. . . . A smile, a touch, confidence and security are still beyond our programming capabilities. . . . We must focus on our distinct human qualities of insight and caring. In this way, the popular view that intensive care is a depersonalizing environment can be replaced by the recognition that human beings are caring for human beings.

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DORRIE K. FONTAINE · SHAWN CODY

CHAPTER 203 ■ USE OF NURSING-SENSITIVE QUALITY INDICATORS

MARGARET LACCETTI AND CHERYL H. DUNNINGTON

INTRODUCTION

Nursing care does make a difference to the patient, to the families, to the healthcare team and in determining patient outcomes. Functions of nursing in the critical care environment include: ongoing assessment of the patient, therapeutic interaction with the family, facilitation of communication across multiple healthcare disciplines, and engaging in activities directly impacting the patient clinical outcome. A critical care nurse is a registered nurse who has been specially oriented and educated concerning the needs and acute physiology of a critically ill patient. Through the application of scientific knowledge, the critical care nurse reacts to the full range of human experiences, within the context of a caring relationship. One focus of nursing care in the ICU is the concept of quality. Quality includes the promotion of safe, efficient, and effective care based on scientific principles demonstrated through evidence that culminates in satisfaction for the patient, family, and the nurse.

The scope of practice for a nurse is determined by the level of formal education or preparation, area of clinical practice, competency validation, hospital or facility policy, and education or training as part of or required for a particular job. Scope of practice may also be mandated by the individual State Board of Nursing or through legislation. Critical care nurses receive more intensive orientation in preparation for patient care, and may be required to hold certifications in areas such as advanced life support. The American Association of Critical Care Nurses has developed a set of standards of care (Table 203.1) and defines the scope of practice for the critical care nurse, using the principles developed by the American Nurses Association (ANA) [1]. Utilization of these standards provides a framework for the delivery of comprehensive, high quality care.

CRITICAL CARE NURSES: PAST TO PRESENT

In 1854, Florence Nightingale was the first to identify the need to segregate the sickest patients needing the most intensive care in an area she referred to as her Monitoring Unit. Here, patients wounded in battle were able to receive nursing care with greater regularity, from women she had trained specifically. Through delivery of more consistent care from better trained nurses, she was able to demonstrate significantly decreased battlefield mortality, from 40% to 2% [2].

Caring for the most critically ill patients separate from other patients allows nurses to meet the complex needs of patients and families. This is accomplished through application of specific training and education with regard to disease process, treatment modalities, and the psychology of devastating injury or illness. Additionally, sequestering critically ill patients for care facilitates changes in nurse-to-patient ratio. A critical care nurse is commonly responsible for the nursing care of one or two patients.

Critical care nursing, as we know it today, emerged after World War II. The increase in medical specialization and improvement of technology influenced the development of this specialty [3]. The first intensive care or critical care units were established in the 1960s. Preparation to care for these patients resulted in development of curricula addressing nurses as well as intensivists, physicians specifically trained in critical care.

Nurses are the largest group of healthcare providers caring for patients daily in the critical care unit. As members of the healthcare team, nurses are responsible to provide nursing and medical interventions, as ordered, and evaluate the effect of those interventions on patients. An enormous part of the demand of patient care is the work of nurses, based on standards of care supported by appropriate resource allocation, enhanced nursing knowledge, accountability, and institutional policies and procedures. Clinical decision making is grounded in evidence-based practice that grows from the nurse's commitment to lifelong learning. Developing and implementing a plan of care allows interventions to be provided in a safe, systematic way, tailored to the condition of each individual patient. As a result of a holistic approach and long periods of time at the bedside in critical care, it is the nurse who gives voice to the patient and family, including them in planning for care. Communication and collaboration among healthcare professionals are essential in planning and delivering care, as well as in maintaining a healthy work environment, one that promotes safe, efficient, effective care for patients. Interdisciplinary communication and collaboration are critical to prevent errors and omissions in the plan of care. The American Association of Critical Care Nurses, in a 2005 study [4], described the consequences of poor communication behaviors among healthcare professionals. These consequences include medication errors, infections, falls, increasing complications of both disease and treatment, and death. Seven areas were specified to be contributing to poor outcome: broken rules, mistakes, lack of support, incompetence, poor teamwork, disrespect, and micromanagement. Participants in this study described a resistance to communicating with others regarding these areas. Only through promotion of enhanced communication can patient safety and improved outcomes be expected. The Joint Commission on Accreditation of Healthcare Organizations identifies poor communication as a primary factor in sentinel events [5]. The Institute of Medicine described communication as a contributor to the harm patients experience in the course of their care [6].

The result of poor nursing care in relation to poor patient outcomes has been evaluated. These poor outcomes result in higher overall cost, low rates of nursing job satisfaction,

TABLE 203.1

CRITICAL CARE NURSING: STANDARDS OF CARE

Assessment	The nurse caring for the critically ill patient collects all data that is pertinent to the patient. This data is collected from the patient, family, and other members of the healthcare team to develop a holistic view of the patient and their issues. Data collection is driven by the priorities of the patient's immediate condition and anticipated concerns for care. The critical care nurse uses analytical models and problem solving tools when collecting assessment data. All relevant data is documented and communicated to other healthcare providers.
Diagnosis	The critical care nurse uses the assessment data to develop diagnosis and care issues directly related to this individual patient. These diagnoses are prioritized according to the immediate needs of the patient.
Planning	The critical care nurse is sometimes seen as the coordinator of the plan of care for the individual patient. They take into account the patients' individualized needs and situation. This care plan is developed in conjunction with the patient, family, and other members of the healthcare team. The plan establishes priorities, provides continuity of care, and considers resources available.
Implementation	Once the plan of care has been developed, it is the responsibility of the critical care nurse to implement the care. The interventions are developed to promote comfort and reduce or prevent suffering.
Evaluation	The critical care nurse must evaluate all plans of care once they have been implemented. They must evaluate the effectiveness of interventions and check if the desired outcome was achieved.

decreased patient and family satisfaction, accreditation issues, and lower rates of reimbursement [7]. For example, cost per case will increase in medical patients with urinary tract infection and pressure ulcers and in surgical patients with urinary tract infection and pneumonia. Provision of safe, high quality patient care is motivated by both professional accountability and growing financial pressure. By evaluating the quality of patient care, opportunities for poor patient outcomes can be eliminated or prevented. Use of Nursing-Sensitive Quality Indicators (NSQI) provides an opportunity to evaluate and improve care in the critical care unit. Quality and Nurse sensitive indicators are defined as measures and indicators that reflect the impact of nursing actions on outcomes. Although the entire scope of nursing-sensitive indicators includes structure, process, and outcome of nursing, nursing-sensitive indicators in critical care are primarily outcome driven.

Nursing-sensitive quality indicators identify and allow measurement of structures of nurse-specific patient care, the processes by which this care is accomplished, and the outcomes of that care. They are performance measures that quantify the work of nursing and the outcomes of that work. These indicators are particularly useful in the critical care setting, where intensive nursing care directly influences patient safety and outcome. In addition to measurement, the use of NSQI promotes identification of best practice and accountability for practice, and points out gaps in research, education, and practice within the discipline of nursing and in interdisciplinary patient care. NSQI, as they measure nursing's impact on the quality of patient care, are instrumental in helping hospitals to reduce misdirection of nursing time to nonproductive or non-patient care tasks or activities. By allowing nurses to engage in the work of nursing, patient outcomes are improved, appropriate staffing decisions are made, and nurse job-satisfaction is enhanced [8].

The American Nurses Association (ANA) Nursing Safety and Quality Initiative began in 1994, aimed at the development of hospital quality indicators. Data from this initiative was stored in the National Database of Nursing Quality Indicators (NDNQI), at the Midwest Research Institute and University of Kansas School of Nursing in 1998. The initial outcome measures included nosocomial infection rate (bacteremia), rate of patient falls with injury, patient satisfaction with nursing care, patient satisfaction with pain management, patient satisfaction with educational information, and patient satisfaction with care. Process measures included maintenance of skin integrity. The NDNQI has developed nationally accepted measures to assess quality of nursing care, identifying and promoting best practice around specific indicators. The database provides members the transparency of quality outcomes, motivating nursing leaders to implement practice that can maintain or improve those outcomes. Current NDNQI indicators can be found in Table 203.2.

NSQI IN CRITICAL CARE NURSING PRACTICE

Infection is one complication critical care patients are particularly at risk for, as the result of invasive procedures, disease process, and exposure to multiple infective organisms. Specific NSQI address behaviors aimed at avoiding this risk. The most common potential infections in the ICU are catheter-associated urinary tract infection, central line related blood stream infection (BSI), and ventilator-associated pneumonia.

Urinary Tract Infections

Catheter-associated urinary tract infections (CAUTI) contribute to almost half of all nosocomial infections, resulting in increased hospital stays and cost of treatment. Placement of urinary catheters in the critically ill patient facilitates determination of urinary output. They are also essential in managing incontinence in the unresponsive or immobile patient, preventing moisture-related skin breakdown. However, an indwelling urinary catheter enhances the risk of UTI.

Urinary catheter care is a direct responsibility of nursing, including proper placement, assessment, maintenance of a closed system, use of aseptic technique when obtaining a urine sample, management of the collecting bag system, and appropriate delegation of tasks. The critical care nurse is well prepared to provide care as necessary for UTI prevention, as well as to delegate care tasks such as catheter hygiene, appropriately and safely to ancillary staff. It has been proposed that one important aspect of CAUTI prevention may include increases in the number of registered nurses (RN) at the bedside to provide patient care. In one study, a large and significant inverse relationship was found between full-time-equivalent RNs per adjusted inpatient day and urinary tract infections after major surgery [9].

Proper placement of a urinary catheter mandates that strict asepsis be maintained throughout insertion. Choice of an appropriately sized catheter is critical in proper placement. The

TABLE 203.2

NDNQI NURSING INDICATORS

Nursing hours per patient day	■ Registered nurse (RN) hours per patient day ■ Licensed practical/vocational nurses (LPN/LVN) hours per patient day ■ Unlicensed assistive (UAP) hours per patient day
Nursing turnover	
Nosocomial infections	
Patient falls	
Patient falls with injury	■ Injury level
Pressure ulcer rate	■ Community acquired ■ Hospital acquired ■ Unit acquired
Pediatric pain assessment, intervention, reassessment cycle	
Pediatric peripheral intravenous infiltration	
Psychiatric physical/sexual assault	
RN/education/certification	
RN survey	■ Job satisfaction scales ■ Practice environment scale
Restraints	
Staff mix	■ RN ■ LPN/LVN ■ UAP ■ Percent agency staff

NDNQI, National Database of Nursing Quality Indicator.

smallest possible catheter to promote bladder drainage reduces opportunities for infection by reducing damage to urethral mucosa during insertion.

Assessment of the patient with a urinary catheter should, at least, address the presence of adequate urinary production, as well as placement of the collecting bag at an appropriate place below the level of the patient's body. The catheter should be secured to the patient's thigh (or abdomen, in male patients only) with a catheter strap or anchoring system to prevent pulling and tugging. Pulling on the catheter can cause damage to the tissue in the urethra. Damage to this area can lead to a bladder infection. Use of skin prep under the anchoring system may help to prevent skin irritation and breakdown [10]. Care of the patient with a urinary catheter includes cleaning the catheter with soap and water or peri spray as part of daily hygiene and following a bowel movement, and avoiding powders and creams on or around the catheter or insertion area. CAUTI prevention is enhanced when the collection bag is emptied consistently prior to moving or ambulating the patient, and maintaining the drainage bag and tubing below the bladder level to facilitate urine flow and prevent backward flow into the bladder. It is important to never place the collecting bag on top of the patient when transferring him to or from a stretcher, as this allows backflow of urine to the patient.

Three main sites of potential infection in patients with a urinary catheter are: along the urethral wall (avoided by providing catheter care), at the junction between catheter and drainage bag if the system is opened (avoided by maintaining a closed system and not disconnecting the catheter from drainage bag), and at the drainage outlet (avoided with appropriate aseptic technique).

Through conscientious and evidence-based nursing care for the patient with an indwelling urinary catheter, it is possible to prevent CAUTI, thereby reducing the patient's risk of increased length of stay in the hospital, infection-related complications, and increased cost of patient care.

Blood Stream Infection

As the result of multiple invasive procedures that will occur in the care of a patient in the critical care unit, as well as conditions or treatments that may compromise the patient's ability to resist infection, the critically ill patient is at greater risk for nosocomial infection. Catheter-related BSIs are one example of an infectious complication that occurs in patients cared for in critical care units. These catheter-related BSIs are responsible for increased healthcare costs, longer critical care unit stays, longer hospital stays, and death.

A central venous line is a catheter that delivers fluids directly into the central circulation. Three primary functions of this catheter in critically ill patients are large volume fluid resuscitation, hemodynamic monitoring, and administration of hyperosmolar intravenous fluids, such as total parenteral nutrition. They may be an alternative when the patient has poor peripheral access, and specifically with multi-lumen catheters that allow for administration of complex medication regimens and solutions simultaneously. In critically ill patients, the advantages of central vascular access over peripheral access are many. Central access allows medications and solutions administered directly into central circulation, promoting rapid systemic distribution. Blood flow at the right atrium or superior vena cava is rapid, large volume, quickly diluting hyperosmolar solutions. The patient's peripheral vasculature is preserved intact for later access, when the patient is no longer a resident of the critical care unit.

Catheter-related BSIs are identified by positive blood culture with the catheter suspected as the infective site clinically or in

light of the microbiology. Through excellent nursing care, the critical care nurse is instrumental in preventing these infections from the process of insertion, attending to aseptic technique during dressing changes and catheter use, and by comprehensive assessment of the site and patient status, as long as the catheter remains in place.

Preventive measures essential for the nurse to facilitate at insertion of a central catheter include appropriate hand hygiene for aseptic procedures, full barrier precautions, and skin preparation with 2% chlorhexidine or the institutional policy driven choice. Use of gloves does not eliminate the need for hand washing.

Regular assessment of the insertion site for drainage, redness, oozing or swelling, and assessment of the dressing for integrity are part of comprehensive nursing care of the critically ill patient. Hub or injection cap contamination is another source of potential infection. Thorough cleansing with an antimicrobial is required prior to every access. Cleansing is mechanical, as well as chemical, and it is important to allow antimicrobial solutions to dry before accessing the port. All connectors should be regularly inspected for integrity, and antimicrobial disinfection should be used at connection sites whenever the closed system is broken. The nurse can also determine when it may be appropriate to remove a central catheter. If a central line is not being used, or the patient's condition or treatments support vascular access peripherally, removing the central catheter may be a good choice to reduce the patient's risk of catheter-related BSI [11].

Given the need for multiple opportunities to utilize vascular access in critically ill patients, multi-lumen catheters are the norm in critical care units. There is evidence that multi-lumen central venous catheters put patients at slightly higher risk of infection compared with single-lumen catheters. However, this increased risk is justified for the critically ill patient by the convenience and improved vascular access afforded by multi-lumen vascular catheters [12].

Finally, documentation is a nursing function vital to prevention, prompt identification, and treatment of catheter-related BSIs. Documentation is a primary form of communication between members of the healthcare team. It provides history and context to clinical findings. Nursing documentation of process and procedure during insertion or use of a central line, and routine assessment findings provide the basis for prevention and early intervention.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is the most common type of hospital-acquired infection, impacting approximately 9% to 27% of all mechanically ventilated patients [13]. VAP can increase the average length of stay for an ICU patient by 7 to 9 days. It may also increase mortality by up to 43% when the patient has an antibiotic resistant microbe [14]. This translates to an additional cost of $40,000 to each hospital stay and can be estimated to cost hospitals $1.2 billion per year. Approximately 50% of all antibiotic use in the hospital setting is for the treatment of VAP [15].

VAP is defined as a pneumonia that occurs 48 hours after mechanical intubation. The endotracheal tube provides a direct link for the bacteria to the lungs. Upper airway and oral secretions pool above the cuff on the endotracheal tube, forming a biofilm that can be dislodged into the lungs during routine nursing tasks such as suctioning, turning the patient, or repositioning the endotracheal tube. The body is unable to prevent entry of these bacteria into the lungs, enhancing the risk of pneumonia. Diagnosis of VAP is based upon radiographic findings, clinical, laboratory, and microbiology results. Symptoms to be considered in diagnosis include fever, elevated white count, and purulent sputum [16].

Nursing plays an integral role in the prevention of VAP. The CDC recommends that all patients receive a pneumococcal vaccine every 5 years, except those who received the vaccination over the age of 65 [17]. Critical care nurses are the front line against the prevention of VAP. It is the care that the bedside nurse provides that has the greatest impact. Things as basic as hand washing prior to patient contact will contribute to prevention.

Mouth care, a basic nursing intervention, is thought to decrease VAP by reducing the amount of bacteria in a patient's mouth. Mouth care is described as not only rinsing the mouth but also brushing the teeth, gums, and tongue to remove plaque. The use of pharmacological agents (such as chlorhexidine) has shown to decrease VAP in the cardiac surgery population, but these protocols remain untested in other patient populations [18].

The old habit of using saline lavages down the endotracheal tube prior to suctioning is related to an increase in the VAP rate. Rather than liquefying secretions, the saline lavage actually dislodges bacteria from the endotracheal tube and pushes the bacteria into the lungs [19].

Turning patients who are intubated on a routine basis not only improves pulmonary status, it also helps prevent pressure ulcers. The position of the patient is critical in VAP prevention; studies have shown that having the bed elevated to between 30 and 45 degrees prevents reflux and aspiration of stomach contents into the lungs [19]. It is imperative to not only have the patient at more than 30 degrees while in bed, but also during transport, or during CT scan or MRI, if it is possible to maintain the elevation of the head of the bed.

The use of standardized orders and clinical pathway guidelines are an important part of the prevention of VAP. All disciplines must be aware of the standards of care and practice to those standards.

Lastly, even in the busiest of ICU's, it is important that the patient's pneumococcal vaccine status be assessed and addressed.

Pressure Ulcers

Pressure ulcers are the direct result of decreased capillary perfusion to the skin and subcutaneous tissues as the result of compression. They range from areas of redness and irritation to frank tissue necrosis. Mortality is related to pressure ulcer development, particularly in elderly patients, with some studies describing rates of mortality as high as 60% in older persons within 1 year of hospital discharge [20]. More often, pressure ulcers occur with changes in health status, particularly as mobility, perfusion, and nutritional status are negatively affected. Pressure ulcers result in increased length of stay and increased hospital costs related to treatment. The Healthcare Cost and Utilization Project, in 2006, determined the average charge for pressure ulcer treatment per hospital stay to be $37,800 [21].

Multiple risk factors are associated with the development of pressure ulcers, including host-specific factors such as nutritional status and disease process and systemic factors such as preventive resources and workload of direct caregivers. Risk factor identification, preventive measures, and treatment of existing pressure ulcers to decrease exacerbation and progression and promote healing are all within the purview of the critical care nurse. Disease states putting the patient at risk to develop pressure ulcers include diabetes mellitus, cardiovascular and peripheral vascular disease, stroke, renal failure, sepsis, febrile illnesses, cancer, and hypotension. Patients who are hypovolemic are at risk because of decreased perfusion, as are

those who are malnourished. Illness states directly affect nutritional status by increasing metabolic need. Any physiologic process that impedes the microcirculation, whether locally or systematically increases the risk for pressure ulcer development. (Smoking is an important contributor to impairment of the microcirculation, so a current smoking history is a significant risk factor to add to the patient's risk profile.)

Previous history of pressure ulcer is a clinical risk indication. Any condition or treatment that impairs patient mobility directly enhances the patient risk, including use of physical restraints. Pressure ulcer development has been associated with low body mass index, where the boney prominences do not have the protective benefit of adipose tissue, and with obesity, where increased weight directly impedes capillary flow and perfusion. Both localized and generalized edema can also contribute to the risk of ulcer development. Incontinence, both urinary and fecal, and diuresis put the patient at risk of moisture-related ulcer development, as will poor hygiene. In the critical care area, the presence of multiple tubes, lines, and catheters also put the patient at risk by adding new areas of perfusion compression. Pressure ulcers form below the nostrils or behind the ears as a result of pressure from a nasal oxygen cannula or elsewhere, when IV tubing or urinary catheters lay under body parts. This short list of risk factors just begins to describe patients in critical care.

The work of the critical care nurse is in both prevention and treatment; the essential starting point is assessment. Preventive assessment includes identification of those patients at high risk to develop pressure ulcers by defining the risk factors present, so that preventive measures can be instituted to address as many of these factors as possible. A variety of tools have been developed for this purpose, with the Norton and Braden scales most popular in hospitals in the United States. Regardless of the tool chosen, the importance is to use it consistently for comprehensive risk assessment and to document and communicate both the findings from the scale or tool and the plans in place for prevention. Additionally, patients at risk must be assessed regularly for areas of redness, poor capillary refill or skin tears, all of which indicate the beginnings of pressure ulcer formation.

Prevention can be especially challenging for the nurse caring for the critically ill patient. Many of the risk factors identified may be directly related to either disease or treatment and may be difficult to modify. Therefore, the consequences of disease or treatment must be considered in the prevention plan. For example, the patient with low body mass index and protuberant boney prominences will be managed through frequent turning, positioning, and use of assistive devices to promote mobility or maintain positioning. Longer term interventions to address nutritional needs may or may not be possible for a particular patient at a particular time.

Considerations for preventive interventions include skin care, hygiene, support surfaces to reduce pressure distribution, nutrition and hydration, and mobility and mechanical loading. Although there is no current agreement on what preventive skin care exactly entails, bathing to promote good basic hygiene, particularly in cases of incontinence, and use of protective or barrier products in areas prone to moisture, friction, irritation, or compression are essential. Barrier skin products are essential to managing pressure ulcer prevention in the incontinent patient, as urine or stool can chemically promote skin breakdown in certain conditions, or complicate pressure ulcers through the potential for infection. The bathing process also promotes mobility, even if only passive mobility, repositioning during bathing and application of skin protection products, and an opportunity to assess for developing ulcers or areas of potential hazard, such as wrinkles or rolls in bedding or tubes and catheters in place underneath the patient's body. It is important to address dry skin as a risk but avoid traditional lotions or creams. They may promote moisture-associated ulcers, and may even promote bacterial growth.

Assessing for and addressing hydration issues are important in the critically ill patient. Hypovolemia or hypotension directly affects capillary perfusion, decreasing oxygen delivery to areas of compression, enhancing the risk for pressure ulcers at those points. Hypervolemia may result in edema, also increasing the risk of compression.

In critical care units, nurses are particularly apt to utilize 'special beds' to prevent skin breakdown. There are a variety of choices currently available, with much variation depending on the facility. However, the goals of any of these special surfaces are redistribution of weight or pressure, reducing incidence of compression and promoting capillary perfusion. As risk factors mount in preventive assessment, the more beneficial a specialized support surface becomes. Little research currently supports which is the best surface to use, and patients with different clinical conditions may have widely different needs. Drawbacks to use of special support surface beds, whether dynamic air or particle beds, or static surfaces such as foam, are expense, availability, and sometimes, ease of use for the nurse.

Enhanced mobility as prevention may include using assistive devices to promote patient-assisted mobility or the traditional nursing approach of frequent turning and positioning. Providing an over bed trapeze for the bedbound patient may give a patient who is strong enough the leverage assistance to be able to move about in bed more frequently. Even maintaining both upper side rails in a raised position when not directly caring for the patient may give him the opportunity to use those side rails as assistive devices in being able to move, sit up, or turn side to side.

For the patient unable to move himself in the bed, turning and positioning at least every 2 hours to reduce compression over potential areas of breakdown over time is essential. A sentinel study evaluating time between repositioning has added to the science of nursing in identifying the 2-hour window as being the most beneficial for most patients [22], but even Florence Nightingale described turning and repositioning her patients in the quest for optimal return to health. Turning and repositioning in a timely fashion can be a challenge in the critical care setting. The patient's clinical condition, as well as equipment used for treatment may impede options for positioning. Patients who are unconscious, paralyzed, or immobile for other reasons may be unable to remain in position once turned or moved. So, it becomes vital for the nurse to use mobility aids and positioning devices to effectively move the patient. Mobility devices may be as simple as using the draw sheet or more sophisticated, such as air driven hover devices or lifts. Although mobility aids protect the patient, just as importantly, they are designed to protect the nurse from injury while repositioning the patient. Once moved, wedges, pillows, splints, or other devices may be used to retain that position. Please be certain that those devices do not contribute to new areas of compression on their own.

With critically ill patients, the most carefully implemented prevention regimen may fail, or the patient who arrives in the critical care unit in a state of progressively declining health may already have one or several pressure ulcers. At that point, using agency procedures or clinical guidelines, cleaning, staging, consistent assessment and restaging as required. A variety of treatment measures including those interventions useful for prevention, are used to prevent exacerbation, stage advancement, and promote healing.

Specialized interventions may include debridement, whether surgically or mechanically, such as the use of a wet to dry dressing. Large ulcers may be treated using wound vacuum dressings to promote closure but retard abscess formation. As pressure ulcers are often particularly painful, assessment and pain

management is another essential part in managing pressure ulcers in the critical care unit.

Falls

More than one third of persons over the age of 65 fall every year, and half of these falls are recurrent. By 2020, the estimated cost related to falls and subsequent injuries is $34 billion dollars [23]. The Joint Commission has identified falls as high risk and requires all facilities to develop a fall prevention program. This initiative was instituted because of the increase of patient deaths due to falls (sentinel events): in 2008, the Joint Commission reported 60 sentinel events related to falls and this trend has been rising since 1996 [24].

While the ICU frequently treats patients post fall, it is important to monitor and prevent falls during their ICU stay. Every patient must be assessed for fall risk upon admission, at least daily and when there is a change in status. Multiple tools are available for assessing risk, such as Heinrich II and Morse scales. All tools consider age, comorbidities, fall history, physical limitations, cognitive impairment, and current medications [25,26]. The majority of all ICU patients classify as high risk.

It is the responsibility of the critical care nurse to identify those patients at risk for falling and institute measures to prevent falls. Based upon assessed needs of the patient, the bedside team needs to initiate measures to prevent falls that may include physical and psychosocial needs as well as environmental concerns.

Addressing physical needs includes provision of adequate pain management, intervention with sensory deficiencies such as sight or hearing, interventions preventing or alerting changes in position of rising from the bed or chair such as wedge cushions, lap belts, or tab (bed exit) alarms. Other interventions to meet physical needs may include repositioning for both safety and comfort, and adequately meeting toileting needs. Toileting includes instituting a schedule based on patient need, frequent offering of assistance, commode or bedpan, and teaching regarding urinary catheterization.

Providing for psychosocial needs includes management of anxiety, frequent reminders to request help before moving about, enlisting the aid of family members or sitters to alert staff-to-patient movement, or using distraction techniques to minimize the effects of the critical care environment.

Environmental issues that may add to the risk of falls in the critical care unit include noise and lightning as well as inconsistent patient observation. Initiatives to control noise, normalize lighting, promote quiet time or rest, or simply moving the patient closer to the nurses' station for more consistent observation may be useful interventions to reduce the risk of falling.

THE CHALLENGE OF FOCUSING ON ONE NSQI AS IT IMPACTS ON OTHERS

Use of NSQI in clinical practice is not just an exercise in measurement, but a true clinical tool in improving patient outcomes. Nurses do, indeed, influence patient care and patient outcomes. Even focus on a single NSQI promotes preventive or health promoting action in other areas of the patient's health, even on other measurable NSQI [27]. Focused nursing measures on prevention of catheter-related urinary tract infections may address issues such as incontinence, directly affecting risk for pressure ulcers. Helping the patient to increase or enhance mobility, finding ways to eliminate catheter need and enhance bladder emptying may also address mobility-associated risks for pressure ulcer formation. Conversely, interventions aimed at preventing VAP may confound or prohibit efforts intended to address another NSQI. For example, maintaining the head of the bed at a 45 degree angle as a preventive measure for ventilator-associated pneumonia may prevent efforts at early removal of indwelling urinary catheter, as the patient is unable to move and position effectively to promote use of a bed pan or urinal, thus putting the patient at greater risk for UTI. The critical care nurse's holistic approach to caring for the patient allows for consideration and balance in prevention and intervention to facilitate optimal patient outcomes through enhancing preventive measures to consider other interventions necessary.

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CHAPTER 204 ■ ROLE OF THE ADVANCED PRACTICE NURSE IN CRITICAL CARE

THERESA R. MACFARLAN

INTRODUCTION

Advanced practice nurses (APNs) are registered nurses prepared at the master's or doctoral level. They function in a multitude of inpatient and outpatient settings across the health care continuum. APN roles include Clinical Nurse Specialist (CNS), Nurse Practitioner (NP), Certified Nurse–Anesthetist, and Nurse Midwife. Though their practice environments, patient populations, specialty knowledge-base and skill sets vary greatly, all APNs share core competencies of direct clinical practice, expert coaching and guidance, consultation, research, clinical and professional leadership, collaboration, and ethical decision-making [1]. CNSs and Acute Care Nurse Practitioners (ACNPs) possess education and expertise in areas that uniquely equip them to practice in the critical care environment. All APN roles require advanced nursing knowledge and skills; the roles are not the same as those held by physicians, although APN practice may be similar to physicians in many medical therapeutic realms [1]. When APNs begin to transfer new skills or interventions into their practice, they become nursing skills, informed by the clinical practice values of the nursing model: "*the advanced practice of nursing is not the junior practice of medicine* [1]."

This chapter describes the Acute Care CNS and ACNP roles, scope of practice, certification, credentialing, and reporting mechanisms. In addition, the science related to outcomes of APN practice and co-practice with other providers is discussed.

ROLE AND SCOPE OF PRACTICE

CNS—A CNS is an expert clinician in a specialized area of nursing practice. The specialty may be defined by a population (women), a setting (critical care unit), a disease or medical subspecialty (cardiovascular disease), a type of care (rehabilitation), or a type of problem (wounds) [1,2]. The CNS approaches the APN role through three spheres of influence: at the patient level in direct care, at the nurse level with staff development, and at the institution level providing oversight of care [1]. Staff education and system change responsibilities represent a large percentage of the CNS's role [1]. In each of the spheres of influence, the primary goal of the CNS is continuous improvement of patient outcomes and nursing care. Key elements of CNS practice are to create environments through mentoring and system changes that empower nurses to develop caring, evidence-based practices. The CNS is responsible and accountable for diagnosis and treatment of health-illness states, disease management, health promotion, and prevention of illness and risk behaviors among individuals, families, groups, and communities [3].

ACNP—Of the APN categories, nurse practitioners (NPs) have undergone the broadest expansion in practice arenas. Emerging from the primary care setting, NPs began to expand their role into specialty and subspecialty areas in response to population changes in health care. Preparing NPs for acute care practice began in the early 1990s as a response to the need for advanced level practitioners in the inpatient, acute and critical care settings. Only ACNPs have been educated and trained to manage critically ill patients in ICU settings, but NPs with other educational preparation (such as family, adult, or gerontology) may practice in other hospital areas. However, this use of other NPs in the acute care setting has been questioned, as their scope of practice (academic preparation and experience) does not always include acute care patient management [4].

Though both CNS and ACNP are targeted to a patient-centered approach to care for patient populations, the continuous on-unit presence of the ACNP at the bedside of patients often differentiates the role of the ACNP from the CNS role [1]. In a 2006 American Association of Critical Care Nurses (AACN) study of APN practice, ACNPs reported spending 74% of their practice time directed toward individual patient management, while CNSs divided their time between nursing personnel (36%), populations of patients (21%), and other disciplines, organizations, or systems (17%) [4]. The primary responsibilities of ACNPs involve activities related to direct management of patient care, accounting for 85% to 88% of time spent in the role [5]. Key elements of the ACNP role include conducting physical examinations and comprehensive health assessments, gathering patients' medical histories, ordering and interpreting the full spectrum of diagnostic tests and procedures, use of differential diagnoses to reach a medical diagnosis, prescribing medications, providing and evaluating the outcomes of interventions, conducting rounds, initiating transfers and consultations, and preparing patients for discharge [6,7]. ACNP care includes health promotion, disease prevention, health education, and counseling as well as the diagnosis and management of acute and chronic diseases [3].

CREDENTIALING

Credentialing is furnishing the documentation necessary to be authorized by a regulatory body or institution to engage in

certain activities and to use a certain title [1]. In all states, APN regulation for practice is based on basic nursing licensure, but many states have additional rules and regulations that delineate requirements and define and limit who can use a specific advanced practice nursing title [1,7]. Nurse practice acts are administered under the authority of state governments to assure public safety [7]. In 23 states, the board of nursing has sole authority over advanced practice nursing; in others, there is joint authority with the board of medicine, the board of pharmacy, or both [8]. Advanced practice nursing certification is national in scope, and it is a mandatory requirement for APNs to obtain and maintain credentialing in most states [9]. APNs must fulfill continuing education (CE) and practice requirements to successfully maintain their national certification, although requirements differ from specialty to specialty. Each advanced practice nursing certification entity clearly lays out the requirements and time frame for recertification. National certifications for most specialties last from 5 to 8 years, and require that the candidate retest unless established parameters are met [1].

Credentialing and licensure for prescriptive authority also occur at the state level. Pharmacology requirements vary from state to state, with most states requiring a core advanced pharmacotherapeutics course during the graduate APN educational program, and yearly continuing education credits to maintain prescriptive privileges [1].

The requirement for APN hospital privileges varies according to the nurse's practice. Many hospitals have different levels of hospital privileges, ranging from "full" privileges to modified privileges for specific functions [1]. A collaborative practice agreement exists between an APN and physician to define parameters of practice for the APN. Many states require this as part of APN licensure [8]. This agreement may take many forms, from a one-page written agreement defining consultation and referral patterns to a more specific prescribed protocol for specific functions based on state statues for APNs. These agreements should be written as broadly as possible to allow for practice variations and new innovations [1].

CERTIFICATION

CNS—Upon completion of an accredited graduate CNS program, certification by examination is available through the American Nurses Credentialing Center (ANCC), or through the certification boards of specialty organizations. The American Association of Critical Care Nurses (AACN) offers a Critical Care Nurse Specialist exam [2]. However, certification exams are not available for many CNS specialties. This is a major regulatory barrier for many CNS specialties in those states that require CNS certification for second licensure [1]. Creating a universal CNS certification examination is in the forefront of current efforts to address this problem. Some states allow prescriptive authority for CNSs.

ACNP—Upon completion of an accredited graduate ACNP program, a national certification exam is available through ANCC or AACN. National certification for acute care nurse practitioner practice began in 1995 [4]. For licensure, many states do not differentiate between NP specialties (such as family and acute care) [1]. ACNPs are granted full prescriptive authority, regulated by state statutory and regulatory bodies [1].

REPORTING MECHANISM

Reporting structures for APNs vary widely within health care organizations [1]. In organizations with many APNs, an APN may report to another APN. In the critical care setting, APNs may report to a nursing administrator responsible for critical care, to a physician, or both. This type of dual reporting may maximize support for the role and clarify role expectations [9]. As licensed independent providers, ACNPs in many institutions must obtain privileges through the credentialing committee. This process may require a designated physician supervisor/collaborator [1]. The degree of supervision needed may change as the APN becomes more experienced in the role.

FACTORS AFFECTING THE GROWTH OF THE ACNP IN CRITICAL CARE

Major factors that contributed to integrating ACNPs into the critical care arena occurred in the late 1990s as a result of a decrease in the number of medical residents and an increase in the acuity of the patient population. Strict guidelines have been placed on resident work hours by the Accreditation Council of Graduate Medical Education (ACGME) and the Residency Review Committee [10]. Instituted in 2003 [5], the 80-hour workweek restriction has especially challenged surgical residents who must balance operative and nonoperative care time in managing critically ill patients [10]. This has contributed to the almost impossible task of providing appropriate level 24-hour intensive care unit coverage by surgical house staff. In a national survey, Gordon et al. [10] found that the use of Physician Assistants (PAs) or NPs may be one effective strategy in allowing surgical residents to care more efficiently for critically ill patients under the new ACGME guidelines. Critical care units that employ ACNPs report being able to meet the ACGME standard for the 80-hour workweek for residency training programs [11]. ACNPs are uniquely equipped to bridge the gap between the nursing and medical models of care, providing seamless continuity of care to patients and their families.

EVIDENCE-BASED OUTCOMES DRIVEN CARE

Evidence-based practice for ACNPs can be described as using the best scientific evidence and clinical expertise to influence patient outcomes [12]. APNs should be adept in the search and critical review of published material, including familiarity with grading systems that indicate the strength of the evidence. Multiple clinical studies have demonstrated cost-containment, decreased days on mechanical ventilation, and decreased length of stay (LOS) as a result of direct APN involvement in managing patients in critical care units [13–20]. Cardiovascular (CV) surgeon and ACNP collaborative practice decreased the LOS for specific diagnosis-related group (DRGs) and decreased total cost for the episode of care when compared to CV surgeon alone. Cowan et al. (2005) [21] demonstrated that physician/NP collaboration focused on enhancing continuity, multidisciplinary team planning, discharge coordination and assessment after discharge, and reduced LOS and hospital costs without negatively affecting readmissions or mortality. In a study that compared outcomes in chronically critically ill patients admitted to a subacute Medical Intensive Care Unit (MICU) who were collaboratively managed by an ACNP/attending physician team or a team composed of fellows and an attending physician, no significant differences were reported in LOS, duration of mechanical ventilation, number of patients who had been weaned at discharge, and disposition [22]. After adding two ACNPs to their trauma service, one teaching hospital was able to obtain compliance with residency work hour limitations by decreasing the average number of hours worked per trauma resident per week from 86 to 79 hours, as well as decreasing

overall hospital LOS [23]. In the area of patient/family satisfaction, NPs have been shown to score higher than resident or attending physicians [24–31]. It has been shown that MD/NP collaboration can enhance continuity of care, multidisciplinary team planning, discharge coordination and assessment after discharge, reducing LOS and hospital costs without affecting readmissions or mortality [21].

COLLABORATIVE PROVIDERS

ACNPs and CNSs sometimes practice collaboratively with other providers in critical care, especially in teaching hospitals and university settings. Brief descriptions of physician assistants and intensivists are included to differentiate clinical roles.

Physician Assistant (PA)

The first formalized physician assistant program was implemented at Duke University in 1965 [32]. PA programs were first developed to augment the practice of primary care physicians, fill service gaps in underserved areas, and help control health care costs [33]. PAs emerged from a medical model of care, as compared to APNs whose identity and practice is shaped by the nursing model of care [34]. The PA role is rapidly expanding beyond primary care to specialty and inpatient practice, including critical care [4].

Intensivists

The Leapfrog Group (founded in November, 2000) recommendations emerged from the growing evidence supporting dedicated intensivist staffing in ICUs. A review of studies revealed that ICUs in which an intensivist manages or co-manages all patients, there were improved patient outcomes, including a reduction in hospitality mortality [35]. Leapfrog recommends at least 8 hour per day intensivist on-unit presence as one of four hospital safety standards supported by evidence-based research. ACNPs provide expert, collaborative care with the intensivists. The AACN has described the importance of effective communication in critical care practice as a core element for patient safety, seamless care, and healthy work environments [36].

CONCLUSION

The complexity of multilayered chronic diseases upon acute illness states, additional regulatory burden for documentation and outcome measurements, the explosion of information and medical technologies, and the astronomical cost of health care poses challenges unforeseen by our nursing predecessors. The enormous workforce and economic burden associated with long-stay ICU patients mandates innovative approaches for their care provision. Nursing practice continues to evolve, striving to keep pace with the needs of an increasingly complex and aging population. Nursing has always been a dynamic profession, evolving with the needs of the population and the capacities of health care systems' resources. Creative visioning and the passion to deliver skilled and compassionate care continue to drive nursing's capacity to meet health care needs. With the current health care crisis of unsustainable cost escalation, it is imperative that healthcare organizations deliver high quality care that is highly efficient and cost effective. Provision of intensive care is one of the largest and most costly aspects of health care in the United States [22]. We are entering a period of unprecedented growth in the number of individuals likely to need ICU services. With current levels of growth, the U.S. health care system will fall far short in the ability even to provide the current level of care, let alone increase the access for the critically ill to intensivists by the year 2020 [35,37]. APN-friendly cultures do not occur by chance, but are created when committed organizations and APNs share common vision and values. An APN friendly culture is one in which all professionals are valued and recognized as possessing unique contributing knowledge and skill-sets necessary to provide excellent, collaborative patient and family-centered care [38]. As we move forward into the uncertain health care climate of the future, ACNPs and CNSs can deliver cost-effective, competent, collaborative, and compassionate care to the growing critical care population.

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CHAPTER 205 ■ INTERPROFESSIONAL COLLABORATION AMONG CRITICAL CARE TEAM MEMBERS

DEBRA GERARDI AND DORRIE K. FONTAINE

"In the ICU, nurses and physicians stand at a patient's bedside initially as strangers, thrown together by a combination of choice and circumstance. With each interaction, they assess one another's knowledge, openness to suggestion, and commitment to patient care. They learn each other's strengths and weaknesses and, over time, forge relationships that become the bedrock of effective collaboration. They communicate, negotiate, and compromise [1]."

INTERPROFESSIONAL COLLABORATION IN CRITICAL CARE

Collaboration among critical care professionals is essential to the provision of safe and effective care in the Intensive Care Unit (ICU). Outcomes associated with effective collaboration include patient safety, improved quality indicators, retention of healthcare providers, and patient and family satisfaction with care. In 1994, a joint position statement was issued by the Society of Critical Care Medicine (SCCM) and the American Association of Critical Care Nurses (AACN) promoting a multidisciplinary approach for managing and providing intensive care services as the preferred model of care [2]. Since that time, an increasing number of mandates and standards issued from national organizations reinforce interprofessional collaboration as a necessary component of care delivery in complex clinical environments.

This chapter describes the principles and importance of interprofessional collaboration, the integration of teamwork as a means of achieving collaborative outcomes, and strategies for cultivating environments in which collaborative delivery of safe patient care can flourish.

DEFINING COLLABORATION

Collaboration is the process of working together toward common goals through joint communication and joint decision-making [3]. Collaboration is both a process and a style that blends high levels of assertiveness and cooperation. Interprofessional collaboration is defined as the process in which different professional groups work together to positively impact health care and relies on negotiated agreements to bring the valued and unique contributions of experts to patient care. Interprofessional collaboration involves understanding what enables effective collaboration as well as understanding barriers to collaboration including: unhealthy power dynamics, poor communication patterns, lack of understanding of one's own and others' roles and responsibilities, and conflicts due to varied approaches to patient care that are inherent within diverse clinical teams [4]. Collaboration is vital, difficult, and learnable [5]. True collaboration is relational and requires skilled communication, trust, knowledge, shared responsibility, mutual respect, optimism, and coordination [6].

COLLABORATION AS A CORE COMPETENCY FOR HEALTH PROFESSIONALS

Health professionals are required to possess core competencies (knowledge, skills, and attitudes) associated with interprofessional collaboration including communication, negotiation, and conflict resolution as a component of academic training

and professional practice [7–9]. The Accreditation Council for Graduate Medical Education and the Association for American Medical Colleges include aspects of communication, coordination, and collaboration among the required physician competencies [10]. Explicit guidelines for collaboration are embedded in professional codes of ethics for nurses and physicians [11,12]. Understanding of and respect for the professional contributions of colleagues across the professions is a necessary precursor to effective collaboration. Slow progress is being made to incorporate these competencies into curricula across the health professions to better teach the concepts of collaboration that support patient safety and improved care coordination [9,13].

MANDATES FOR INTERPROFESSIONAL COLLABORATION

The need for improved interprofessional collaboration has been discussed for decades among professional associations—particularly among critical care associations. The past decade has seen a shift from discussion to concerted action, as multiple calls for improvement in care delivery from the Institute of Medicine (IOM) have emerged, resulting from data linking poor clinical outcomes to ineffective teamwork and inadequate care coordination [14–16]. There is substantial evidence that the leading contributors to medical errors and unsafe care are breakdowns in teamwork, communication, and the overriding culture of health care itself [17,18]. Hundreds of billions of dollars are wasted on medical errors and ineffective care coordination each year [19]. In addition to poor patient outcomes, ineffective collaboration has been linked to perceptions of hostile work environments [20], low morale, and job stress among health professionals [21], increased turnover of clinical staff [22], and moral distress [23]. As such, new mandates are emerging to focus attention within healthcare organizations on strategies for developing interprofessional collaboration as a component of safe patient care.

The National Quality Forum (NQF) added teamwork training and interventions to their 2006 consensus report, Safe Practices for Better Healthcare, which are now represented in the 2009 Report as Safe Practice #3—Teamwork Training and Skill Building [24]. The Joint Commission, through their Patient Safety Goals [25], their sentinel event alerts [17], and their accreditation standards, requires improved teamwork, collaboration, and conflict management across the healthcare organization. Calls for conversation and dialogue to begin to address the challenges to working together are growing [26–28]. With this increased interest comes a growing database of empirical evidence associated with teamwork, collaboration, and improved conflict management in the clinical setting. This culture shift creates a golden opportunity for researchers interested in elucidating the impact of professional subcultures, human factors, team training, and conflict dynamics on the effectiveness of interprofessional collaboration and its impact on clinical outcomes, quality of work environments, and the resilience of health professionals.

INTERPROFESSIONAL COLLABORATION—EMERGING RESEARCH

The complexity of delivering critical care services requires ongoing integration of skills and knowledge from multiple professions. Emerging research highlights several areas including: perceptions of health professionals; the impact of collaboration and teamwork on clinical outcomes, quality indicators, retention of health professionals, patient satisfaction, and the quality of the work environment; characteristics of effective teams; and the influence of conflict on team effectiveness. Much of the research is based on self-reports combined with only a few observational or controlled trials. Several key studies will be reported here that serve as the foundation for future strategies.

Perceptions of Health Professionals

Physicians and nurses often state the importance of collaboration, communication, and cooperation in delivery of clinical care. Until recently, however, there has been little evidence as to how each of the professions defines these key components of the practice environment. In a 2009 study, health professionals indicated understanding and appreciation of professional roles and responsibilities, and communicating effectively to be two core competencies necessary for patient-centered collaborative practice [29]. Studies where both physicians and nurses were queried about collaboration and communication in their specific units suggest that their perspectives are often far apart. Using the Safety Attitude Questionnaire, Sexton and colleagues found that nurses' and anesthesiologists' perceptions of teamwork in the operating room were significantly lower than that reported by surgeons in the same area [30]. One study measuring communication in four ICUs in the United Kingdom noted that, while a majority of senior physicians reported a highly positive open communication style between nurses and physicians, only one third of nurses reported the same [31]. Thomas et al. investigated critical care nurses and physicians' attitudes about teamwork in eight ICUs in six hospitals. Findings of the 320 subjects suggested that while over 70% of physicians viewed collaboration as very high, only one third of the nurses felt the same [32]. These studies indicate that the two professions experience the organizational climate very differently. This begs the question, what underlies these varying perceptions, given that those surveyed were working together in the same units?

A review of the various codes of ethics for the professions of nursing, pharmacy, medicine, occupational therapy, social work, physical therapy, respiratory care, and chaplaincy indicate that the levels of ethical responsibility associated with interprofessional practice fall into five categories: professional conduct (citizenship), acknowledgement of others, cooperation, collaboration, and conflict engagement. The categories reflect a progression in depth of professional engagement and they provide a glimpse into the perceptions each profession acquires regarding interprofessional practice [33]. The discrepancy highlighted in the studies above suggests that differing approaches found in the professional codes of ethics may impact the way in which each profession is defining and perceiving collaboration. This idea proves likely based on the results of a 2006 survey measuring teamwork among nurses and physicians in the OR (operating room) setting. Discussions with survey respondents indicated that, "nurses often described good collaboration as 'having their input respected,' whereas physicians often described good collaboration as having nurses, 'who anticipate their needs and follow instructions' [30]." Research into effective teamwork indicates that having shared mental models and a common language are key for working well together. A good starting point for enhancing collaboration is the joint development of shared models for collaboration that provide a common language for working together.

Impact on Quality, Safety, and Retention

Research that examines the impact of interprofessional teams on patient safety is limited. Most reports either are anecdotal

or include a limited description of the methods used to measure team effects [16]. A 2009 Cochrane review of clinical trials measuring the impact of interprofessional collaboration practice-based interventions designed to improve the work interactions or processes among various types of health professionals yielded five studies that fit the review criteria [4]. The five studies evaluated the effects of interprofessional rounds, interprofessional meetings, and an externally facilitated interprofessional audit. Three of the studies found that the interventions led to improvements in patient care, such as drug use, length of hospital stay and total hospital charges, while one study showed no impact, and one study showed mixed outcomes. The results of other studies suggest a positive correlation between interprofessional practice and clinical outcomes. Recent studies looking at the impact of teams in critical care and primary care have linked teamwork to increased survival to discharge, decreased readmission to the intensive care unit (ICU), fewer adverse events, shorter lengths of stay, and decreased mortality rates following surgical interventions [34]. Research assessing system failures in ORs and ICUs found that positive perceptions of team coordination among ICU staff were associated with lower error rates, that is, when the staff perceived timely transfer of information, role clarity, and awareness of team member activities [35]. Thomas et al. assessed the relationship between teamwork and noncompliance with neonatal resuscitation standards in 132 videotaped resuscitations and found a weak correlation between team behaviors (information sharing, inquiry, treatment planning, and leadership) and compliance [36]. There is also evidence that good team behaviors are linked to decreased turnover among nursing staff in the OR [30] and survey research has shown a link between high levels of cooperation between ICU nurses and physicians and reports of staff burnout [37]. Greater perceived relational coordination has been associated with patient perceptions of higher quality of care, less postoperative pain, greater postoperative functioning, and shorter length of stay [16].

The 2004 Institute of Medicine report, *Keeping Patients Safe*, addresses the work environment of nurses and its impact on patient safety. The report provides an extensive review of the literature on interprofessional collaboration in its *Appendix B: Interdisciplinary Collaboration, Team Functioning, and Patient Safety* [16]. Additional research is needed to differentiate the impact of team behaviors, organizational context, team composition, and team stability on clinical outcomes. In addition, the next phase of research should further elaborate strategies for cultivating team effectiveness [34].

Interprofessional Collaboration and End-of-Life Care

End-of-life care in the ICU is a complex and oftentimes an emotion-filled, process. Much work has been done to examine how to improve end-of-life care. In a 2005 special report from the Hastings Center, three areas were identified as needing greater attention to improve end-of-life care. The authors suggested a rethinking of assumptions related to (i) the end-of-life care delivery system, (ii) the approach to advance directives and surrogate decision making, and (iii) how to manage conflict and disagreement [38]. Each of these has implications for collaborative practice among ICU team members. Difficulties for clinicians in providing end-of-life care include: variability in practice, poor communication among providers, lack of consensus regarding plan of care, incomplete documentation, and differences of opinion regarding the definition of futility [39]. According to a statement released from the Consensus Conference in Critical Care, "The principles of shared end-of-life decision making between patients, family members, and clinicians can be achieved only through full participation of all ICU healthcare professionals in the communication and decision-making process [40]."

Critical care nurses have consistently described one of the greatest stressors in their work to be related to decision-making regarding futile treatment [41]. The most important factor enabling nurses to move from cure to comfort-oriented care is developing a consensus about the treatment plan. A survey of 864 critical care nurses revealed barriers to good end-of-life care as being disagreement about the direction of the dying patient's care, actions that prolonged a patient's suffering, and physicians who were evasive and avoided talking with patient's families [42]. When nurses believe that they are powerless to impact decisions related to a course of treatment they perceive to be unethical or harmful to the patient, it leads to moral distress [43]. According to the American Association of Critical Care Nurses, moral distress has a significant impact on the clinical work environment. Studies indicate that one in three nurses experiences moral distress and in one study, nearly half of the nurses surveyed left their unit, and for some their profession, as a result of moral distress [44]. Incorporation of shared goal setting, protocols for managing end of life care, collaborative decision-making processes, and interprofessional dialogue related to complex cases can alleviate some of the stress experienced by all clinicians in the critical care environment and improve care for patients and their families at a very difficult time in their lives.

STRATEGIES FOR ADVANCING INTERPROFESSIONAL COLLABORATION

There can be no assurance of safe, effective, quality care without collaboration that begins with a trusting, respectful relationship. Addressing what some consider these "soft" issues may in reality be the solution to many of the hardest challenges in critical care settings. In the complex environment of the ICU, the challenge to focus full attention on the patient experience and create systems of care where clear communication from respectful collaboration is the norm is crucial [45]. The history of critical care in the United States is replete with the concept of teams and reliance on expertise from many professionals—the hallmark of the ICU [46]. Relationship-centered care, where the primacy of relationship of patient and healthcare provider exists, cannot occur without skilled partnerships of all members of the healthcare team, especially physicians and nurses [47].

Given the broad impact of interprofessional collaboration and the growing application of teamwork to provision of critical care, it is important to better understand the current strategies for advancing collaborative practices and team effectiveness. Bronstein describes a model for interprofessional collaboration that includes: interdependence, professional activities (work structures and acts), flexibility in traditional roles, collective ownership of goals, and reflection on process (how well the team is working together) [48]. Reader et al. in a review of the literature linking teamwork to outcomes in intensive care generated a performance framework categorizing the various team behaviors that had an impact on clinical care. These behaviors can be categorized as: team communication, team leadership, team coordination, and team decision making [49]. Clarifying models for observing and evaluating collaborative practices provides a baseline for improving performance and elucidating what works. An overview of some of the emerging areas of interest associated with interprofessional collaboration is described below.

Attitudes and Attributes Indicative of Effective Interprofessional Practice

A blend of relational qualities, personal characteristics, skills, and activities constitute collaborative practice. The give and take between team members is in constant flux and resides within the context of the organizational environment. Team factors are divided into task, process, and relationship components. Processes include methods for communicating and sharing information, managing conflict, goal setting, and decision-making. Relationship factors include trust, respect, shared mental maps, status differentials, and attitudes toward teamwork [33]. Increasing emphasis on relational aspects of teamwork is emerging as principles from complexity science further define the necessary elements for high quality care in complex systems. In a study assessing factors that contribute to higher quality outcomes in complex primary care practices, Lanham et al. found trust, mindfulness, heedfulness, respectful interaction, diversity, social/task relatedness, and rich/lean communication to be important factors for the emergence of high-quality care. In addition, they determined that effective reflection, learning, and sense making were requisite behaviors among members of the clinical team [50].

Research indicates that attitudes toward teamwork impact the presence of collaborative practice [51]. Favorable attitudes toward team performance and collaborative patient management approaches maximized team outcomes [16]. There is a significant amount of literature addressing the relational aspects of trust and respect as components of collaborative practice [52]. The Society for Critical Care Medicine describes the attributes of interprofessional teams to be: trust and transparency, collaboration and communication, appreciation of complimentary roles for a shared purpose, leadership, action, and accountability [53].

Team Effectiveness

Collaborative patient-centered care is associated primarily with work in interprofessional teams [54]. In addition to the attitudes and attributes necessary for teamwork, there are specific skills and processes that enable a diverse collection of professionals to work in concert to provide care to critically ill patients. High functioning teams are characterized as having good communication, low levels of interpersonal conflict, high levels of collaboration, coordination, cooperation, and participation [34]. Team coordination is the concerted and synchronous performance of patient care tasks by team members. Coordination requires each team member to maintain an awareness of the work accomplished by the others on the team [49].

Collaboration, as an ongoing process, occurs across a continuum requiring a range of skills for engaging at various levels of depth and nuance. These skills include the capacity for self-reflection, the ability to communicate effectively across professional groups, the ability to give and receive feedback and engage in shared decision-making, consensus building, and the ability to engage in and resolve conflicts [33]. Work processes that support engagement across this continuum are essential as is effective team leadership.

A great deal of research has been conducted on teamwork and team behaviors. One model that has emerged as a foundation for addressing team performance is the Salas framework. This model specifies five core aspects of teamwork which include (i) team leadership (formal and informal), (ii) collective orientation (cohesiveness, common goals, and team success), (iii) mutual performance monitoring (awareness of others and understanding and appreciation of various roles), (iv) backup behavior (helping one another), and (v) adaptability (ability to adjust strategies and resources on the basis of situational assessment) [55]. These areas of teamwork are supplemented by three coordinating activities that include (i) establishing shared mental models, (ii) closed loop communication, and (iii) mutual trust. This model serves as the foundation for the evidence-based TeamSTEPPS training curriculum developed by the Department of Defense and the Agency for Healthcare Research and Quality (AHRQ) [56].

The construct of "team" has multiple definitions. In a recent literature review assessing the impact of teams on clinical and organizational effectiveness, team was defined as, "a collection of individuals who are interdependent in their tasks, who share responsibility for outcomes, who see themselves and who are seen by others as an intact social entity embedded in one or more larger social systems (for example, business unit or corporation), and who manage their relationships across organizational boundaries [34]." Impacting team effectiveness is the continuous morphing of team membership. The idea of team in a traditional work setting is much different in the clinical setting where shift changes, floating, locum tenens, trainee rotations, cross-covering, consultation, procedural specialists, and interdepartmental support staff all impact team configuration at any point in time. This dynamic creates challenges for communication and development of trust among team members. The forming and re-forming of the team requires establishment of relationships on an ongoing, quick-time basis [57]. Team dynamics and organizational complexity require clear communication among team members and effective methods for collaborative decision-making.

Team Communication and Decision Making

Physicians and nurses speak different languages, approach patient care from different frames of reference, and carry out their work very differently from each other (shift work vs. case-based work). The holistic model of nursing, with its emphasis on relational practice and sensitivity to patients' needs as primary, is a different framework from the scientific and objective model of medicine and its emphasis on disease process and diagnosis. As such communication difficulties are predictable. Schmitt identifies the key interprofessional communication patterns that contribute to errors in diagnosis and treatment as (i) counterproductive hierarchical communication; (ii) disjunctions in distribution of authority, responsibility, and accountability across disciplines; and (iii) issues of lack of respect and lack of clarity with regard to legal and ethical obligations across disciplines [58]. Additionally, nurses and physicians evaluate each other's competence in different ways. In a study reported by Schmalenberg et al., physicians tended to judge the competence of the nurses by the quality of the information given, particularly in emergency situations when the patient's condition had changed. Nurses tended to judge the competence of the physician by patient outcomes and the absence of complications, consultation with the nurse prior to writing orders, and the extent to which the physician listened and collaborated in determining the patient's plan of care [59,60]. The need for bridging these world views to ensure effective communication and decision-making is obvious. A look at communication patterns during patient care rounds demonstrates both the status differential between physicians and nurses and the differing perceptions of information sharing. In a 9-month study in which researchers observed 2,391 intensive care interactions, it was noted that nurses made only 12% of comments during rounds and only 10% of the team discussion was directed toward the nurses [61]. The observed nurses were asked their opinion by the medical staff only four times in the nine-month period, and

when interviewed, the nurses portrayed themselves as assertive during rounds. Physicians rely on the surveillance function of nurses who are present with the patient a larger portion of the time and they rely on timely reporting of information by the nurse to make critical treatment decisions.

Team communication is the ongoing sharing of information, ideas, and opinions among members of the team. Reader reviewed 35 studies on teamwork in the ICU and found that errors in patient care occurred most often when team communication failed, particularly after shift change and handoffs, with 37% of the observed errors associated with nurse/physician communication [49]. In a 2008 survey of over 5,000 critical care nurses, 40% of those responding rated communication with physicians as only fair or poor with close to 60% noting verbal abuse [62]. Pronovost and colleagues analyzed ICU adverse event and critical incident data and found that critical incidents were associated with reluctance among nursing staff to report observed errors and patient care issues, a lack of communication between physicians and nurses regarding changes in treatment, inaccurate transfer of information between ICU teams, and inadequate information transfer when new patients were admitted to the unit [63].

Such results have led to initiatives that help the various professions communicate more effectively with each other. These include the use of electronic medical records, practice protocols, procedural checklists designed together by the team, and the use of SBAR for reports from one clinician to another. SBAR, which stands for Situation-Background-Assessment-Recommendation is a script developed by the military as a means of communicating necessary information in a concise and uniform manner so that the receiver of the information can make prompt decisions in response [64]. These efforts help to reinforce the aspects of effective teamwork identified previously including shared mental models, collective orientation, and closed loop communication.

Team decision-making occurs as information and perceptions from the various team members are integrated. Decisions can be made together as the members confer or may be made by the team leader on behalf of the team [49]. Complex decision-making requires the integration of divergent viewpoints within the team that represent a rich array of perspectives, experience, and information. Negotiating through the differences to come to agreement regarding the plan of care is an essential skill for critical care teams. Doing so is dependent upon the relational factors previously described including trust and respect. Teams that adopt competitive, rather than collaborative approaches are not only less effective, but they also create environments in which there are lower levels of team member satisfaction [65]. When negotiations are cooperative, team members are better able to remain flexible and open to the ideas of others leading to more creative problem solving. When conflict levels are high and negotiations are competitive, cognitive flexibility decreases and defensive postures prevent effective collaboration. Team member support for team decisions is predicated on the perceived level of procedural fairness experienced during the decision-making process [16]. Those teams where senior members seek out and incorporate the perspectives and opinions of junior members are more likely to have members who remain engaged with the group, follow through on team decisions, and who continue to be cooperative in future negotiations.

Self-Reflection and Self-Correction

Effective critical care teams are capable of giving and receiving feedback among the various team members and they are able to self-correct, that is, adapt their actions to changes in the patient's condition or to changes in team performance [55]. Reflective practice enables clinicians to evaluate their own responses to situations and to identify areas that need attention. Reflective practice techniques have increasingly been integrated into the teaching of communication skills in medical schools to improve clinician–patient interactions [66]. Developing team practices that allow for self-reflection, observation, and evaluation of group process, and incorporation of what is learned into performance improvement activities, greatly enhances team effectiveness and develops improved trust as the team discovers what qualities and activities enable them to function effectively. Mechanisms for reflecting on performance include: use of team debriefs, case reviews, facilitated reflection with mentors or coaches, and informal conversations among team members.

Professional practice entails continuous learning and adaptation as feedback is received to improve performance and provide increasingly sophisticated care. Improving clinical abilities is just one aspect of self-corrective behavior. A more difficult component of professional practice is the giving and receiving of feedback among colleagues, particularly feedback related to professional conduct and team behaviors [45]. In the seminal 2005 study, *Silence Kills*, researchers sampled critical care staff and physicians in 13 ICUs nationwide. The researchers discovered that the majority of critical care staff and physicians surveyed had concerns about competence of some of their colleagues, had witnessed shortcuts and mistakes, and had experienced disrespect and insufficient team support with very few speaking up to address these concerns [67]. The reasons given by those surveyed for not speaking up include: fear of retaliation, lack of conflict skills, deference to authority, and the belief that nothing will come from speaking up. Avoidance of these difficult conversations led to elaborate workarounds, by physicians and nursing staff, which compromised patient care. In most cases, team members were aware of a colleague's poor performance, often for over a year, and they allowed it to continue rather than provide the necessary feedback needed for improving performance.

Failing to address clinical performance is not the only area of difficulty for health professionals. In July 2008, the Joint Commission released Sentinel Event Alert #40, *Behaviors that Undermine a Culture of Safety* [17]. The alert cites evidence of the correlation between intimidating and disruptive behaviors and the incidence of medical errors and preventable adverse events, patient satisfaction, costs of care, and retention of qualified personnel. The alert goes on to indicate that there is a history of tolerance and indifference to such behaviors and that failure to address these behaviors at both the individual and system levels contributes to unsafe care.

Increasingly, research indicates a large prevalence of unprofessional conduct that could contribute to patient harm. Such behavior also impacts the quality of the work environment. The results from Rosenstein's studies indicate that more than 90% of clinicians surveyed felt that disruptive behaviors invoked feelings of stress and frustration, with more than 80% feeling that disruptive behaviors caused a loss of concentration, reduced team collaboration, and impaired information transfer. In addition, more than 90% felt that disruptive behaviors contributed to poor communication and impaired nurse–physician relationships [68]. A 2009 study among experienced labor and delivery nurses indicates that despite their knowledge of proper clinical actions based on evidence and national practice standards in five high-risk scenarios, the nurses chose to delay or work around the physician when the physician was difficult to deal with. This was particularly true when the nurses believed that their manager or hospital administration would not back them up [69].

The findings of these studies add to the growing literature base that calls for a reexamination of what it means for nurses and physicians to authentically collaborate for patients

to receive expert coordinated care. Improving the capacity of clinicians across the professions to engage in conflict situations and give difficult feedback to colleagues is an essential step in improving the safety of patient care and the quality of clinical work environments [26]. Since January 2009, the Joint Commission has required accredited healthcare organizations to (i) develop a universal code of conduct, (ii) implement a process for dealing with lapses in professional conduct, and (iii) to develop and implement a conflict management process for addressing conflicts among the three top leadership groups (executives and senior management, medical staff, and the governing body) [70]. This increased focus on improving conflict management in the clinical setting is a powerful step in helping to cultivate conflict competent organizations.

Conflict Competence Among Team Members

In addition to managing day-to-day team processes, critical care teams must also manage the competing agendas that inherently exist in interprofessional teams [71]. Just as with perceptions of collaboration and communication, there are differing perspectives among physicians and nurses regarding the presence of conflict. "Studies indicate that physicians do not always recognize nurses' perspectives on conflict. In a study of conflict in intensive care units, nurses identified nearly twice as many conflicts as were identified by both the physician and the nurse [72]." Again, developing a shared mental model of conflict and developing the skills of team members to constructively engage with each other is crucial.

Health professionals identify high levels of conflict in the workplace and much of that conflict is with each other. In a 2009 survey sent to 13,000 physicians and nurses, nearly 98% of the survey respondents reported witnessing behavior problems between doctors and nurses in the past year, with 30% indicating they saw such behaviors weekly and 10% indicating daily occurrences [73]. Among ICU intensivists responding to a survey published in 2009, 70% reported conflict in the past week, with half of the incidents perceived as "severe" and those reporting indicated that the conflict was associated with increased job strain [21].

Physicians and nurses identify a desire for increased opportunities for training and open dialogue that focuses on teamwork and conflict engagement [74,75]. Expertise in conflict management ranges from novice to expert and incorporates capacity for addressing personal conflict, as well as skill in facilitating and mediating conflicts among others. Foundational to skill acquisition is the development of non-adversarial (dialogic) mindsets, cognitive roadmaps for approaching conflict, and expanded capacity for self-reflection and self-correction of ineffective behaviors [76]. Maine Medical Center in Portland, ME and the UMass Memorial Medical Center in Worcester, MA are examples of institutions that have invested in systematic communications training for healthcare providers, leading to sustained improvements in safety and quality [77].

Difficulties that can contribute to conflict within the team include role boundary issues, perceptions of unfair decision-making processes, autonomy versus team needs, feeling that one's contribution is not valued, miscommunication of information, and inappropriate use of hierarchy [78]. Not all conflict is bad and in fact conflict is often necessary for obtaining the best decisions in complex cases. Evidence of the impact of variable types of conflict indicates that some types of conflict (task-related) can improve social capital (trust) within the team and thereby improve coordination of patient care [79].

Conflict within the critical care team may be associated with serious medical errors. An analysis of a national survey of over 6,000 residents (multispecialty sample) indicated that just over 20% reported "serious conflict" with another staff member with nearly 10% of those conflicts being between the resident and nursing staff, and 10% being with another resident. Among those residents who reported no conflict with professional colleagues, 23.8% reported having made a serious medical error, and among those who reported conflict with two or more colleagues, the serious medical error rate was 51%. Further research is needed to determine the empirical association but the significant difference in error rates is enough to prompt further attention [80].

Developing conflict competence across the clinical team to better manage interpersonal conflict is a key aspect of effective team performance. Training and coaching can help to develop conflict engagement skills that enable productive conversations around difficult issues [76]. In addition, ensuring that team leaders and senior professionals model constructive conflict behaviors is even more powerful as a means of embedding conflict competence among team members. Assisting team members and team leaders by incorporating system-wide policies that address conflict and unprofessional conduct provides a starting place for difficult conversations to occur. In addition, embedding conflict experts within the organization whose job is to help facilitate or mediate disputes is another means of supporting safe patient care.

Team Training and Simulation

The growing emphasis on teamwork and interprofessional practice within academic training will have a positive impact on future generations of clinicians. However, there is a lack of team orientation and skills among practicing clinicians. To respond to this need, many organizations are implementing team training and simulation to help promote safe care and more effective clinical coordination, particularly in complex or high risk areas such as the OR, ICU, ED, and Labor and Delivery [81]. In 2007, the AHRQ launched a national effort to support team training to improve communication and teamwork skills among health professionals [56]. Known as TeamSTEPPS™, the program curriculum reflects more than 20 years of research and applied knowledge from other industries including aviation, nuclear power, and the military. Another approach for improving team skills is the use of high fidelity simulation in which clinical teams are given scenarios to enact within a highly sophisticated simulation environment, much as astronauts or pilots would do. The simulations are videotaped and the clinical scenario is adjusted during the training session to assess not only clinical knowledge but also team skills, leadership, and crisis management. Debriefs following the simulations provide for a discussion among team members as to what worked and what could be done to improve performance. Designing training programs that provide for interprofessional learning promotes collaboration and understanding of roles, concentrates the group's efforts toward the needs of patients, and promotes development of trust and respect within the team [82].

Organizational Supports for Interprofessional Collaboration

Even teams that have excellent skills in communication, decision-making, and clinical expertise need support from the organization in which they reside. Design of work processes, policies, and the broader culture of the organization all play a role in supporting effective collaborative practice. Intentionally developing team leaders and supporting them with mentors and

coaches is one means of organizational support [83]. Additionally, creating dyadic leadership models, or "productive pairs," in which there is co-leadership of the ICU by both a medical director and a nursing director, can provide direct support to the clinical teams and also provides a means for modeling interprofessional collaboration and setting a culture of collaboration within the unit. A joint task force from the American Association of Critical-Care Nurses (AACN) and the Society of Critical Care Medicine (SCCM) developed a collaborative practice leadership model in 1983 that resulted in 10 principles outlining the interdependent nature of the two professions in the critical care environment and also outlined the complimentary roles of the two leaders [84]. Such partnerships enable the leaders to more fully address the complex integration of competing demands that range from clinical operations to financial management, risk management, and professional development of new clinicians.

Broader efforts to embed effective interprofessional collaboration across the entire healthcare organization are also underway. The ANCC Magnet certification process specifically emphasizes effective collaboration practices and communication among the professions and those organizations seeking this coveted designation must demonstrate what they have done to ensure adequate mechanisms are in place [85]. Research evaluating nurse–physician relationships within Magnet hospitals has demonstrated better relationships and more collegial work climates than non-Magnet designated hospitals [28]. Hospitals celebrating their Magnet credential now number over 300 with many more seeking certifications.

An innovative model developed to support interprofessional collaboration across the medical center has been implemented by the University of Virginia and makes use of the social technology Appreciative Inquiry [86]. Initiated in 2005, the Center for Appreciative Practice has developed collaborative efforts by the Schools of Medicine, Nursing, and the Health System as a method of supporting ongoing efforts to identify what works best using an appreciative focus. This enables professionals to develop solutions together while enhancing their appreciation of the accomplishments and contributions of colleagues from other professional groups. Such innovative approaches are highly indicative of organizational cultures that fully support interprofessional collaboration and the impact it can have on improving patient care and the quality of work environments.

PERSONAL WELL-BEING AND RESILIENCE

Collaborative environments are not only good for patients, but they also support the well-being of the health professionals who provide care to the seriously ill. A growing area of research related to resilience and personal well-being emphasizes the importance of self-care and collegial support as a means of providing safe care and enabling health professionals to continue in their work for the duration of their career. In a study published in 2008, residents from nine separate residency programs indicated that personal well-being not only impacted the quality of their work, but that high levels of personal well-being resulted in greater patience and collegiality with other health professionals and that low levels of personal well-being contributed to increased interpersonal conflict with colleagues [87]. The residents cited the ability to talk with colleagues as one means of maintaining their sense of personal well-being. Surveys of ICU and OR physicians and nurses indicate that the majority of them seriously underestimate the effect of stress on their professional performance and the likelihood of making an error [16]. Increasingly, emphasis on interprofessional collaboration as a means of improving resilience will emerge as health professionals look for ways to decrease stress, better manage conflict, and effectively navigate the growing complexity of healthcare organizations.

CONCLUSION

There is a growing emphasis on interprofessional collaboration in critical care environments as a means of improving the safety and quality of patient care, to support the development of healthy work environments, and to further the resilience and well-being of health professionals. A great deal more research is needed to further these efforts. Training and academic preparation that reinforces team skills and an appreciation of the contributions of the various professions provides a first step in the promotion of effective collaboration. The development of new models for implementing clinical teamwork, joint leadership, and organization-wide supports will continue to shift the culture of health care toward one in which the various professions are working together, and not just side-by-side.

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CHAPTER 206 ■ HEALTHY WORK ENVIRONMENTS: NECESSARY FOR PROVIDERS AND PATIENTS

KATHLEEN M. McCAULEY

Envision the following scenario: you are a recent graduate of your basic educational program or fellowship, have successfully passed your boards and certification examinations, are armed with superb references from your mentors and faculty, and have identified two job openings in which you can work with the leaders in your specialty. The locations are perfect, close enough to family and friends, and the salary is competitive. You have scheduled interviews at each site and are excited about the opportunities to launch your career and are ready to convince the interviewers that you are the perfect new addition to their team. Your mentors have coached you in competitive strategies to stand out from the other applicants. Given that both interviewers are eager to hire you, how will you choose?

In launching a new career or accepting a new position to further an established career, clinicians would be wise to consider the health of the work environment as important in their final decision. The responsibilities of succeeding in a complex healthcare provider role coupled with demands of personal lives, particularly when complicated by caring for children and/or aging parents, contribute to stress. An analysis of sources of stress for women physicians revealed that expectations at both work and home were key factors, but also that the quality of the work environment was important as well [1].

Results of an expanding body of research and anecdotal reports from a wide range of stakeholders argue that the health of the work environment is critical to both professional satisfaction and patient outcomes. In this chapter, the consequences of toxic work places and knowledge about characteristics of healthy work environments will be reviewed. Differing communication norms between physicians and nurses, inaccurate perceptions about the reality of the ways that team members contribute to critical patient care decisions, significant deficits in conflict management skills, and tolerance for disrespectful treatment of colleagues all contribute to unnecessary and dangerous tension in the workplace that can harm patients. This chapter presents strategies for creating healthy work places, including widespread adoption of national standards.

A sense of what constitutes a toxic versus healthy work environment was clarified by Heath and colleagues [2]. They conducted a series of focus groups with nurses, who were asked to consult with multiple colleagues prior to their discussion. Consensus emerged that toxic environments lack effective communication as well as trust. Hazing behaviors were reported in toxic environments that included withholding critical information, setting each other up to fail, and sometimes actual physical violence. When there is a lack of vision and leadership, arguments over conflicting values are common. In toxic environments, poor behavior is exhibited by all healthcare providers and these problematic behaviors extend to patients and families both as perpetrators and victims.

In times of documented shortages of key healthcare providers, work environments that drive talented clinicians from direct care roles require serious attention. In a study examining job satisfaction rates of nurses in the United States (U.S.), Canada, England, Scotland, and Germany, Aiken and colleagues found that with the exception of German nurses, job dissatisfaction was high, ranging from 33% to 41%. These dissatisfaction rates are much higher than those reported by other professional (10%) and general workers (15%). Of particular concern is the effect of the work environment on younger nurses since one out of three U.S. nurses in this study planned to leave the hospital job within the next year [3]. Factors contributing to job dissatisfaction included insufficient staff to deliver high quality care or simply to get the work done, inadequate support services, failure of administrators to listen to nurses' concerns, minimal opportunity to participate in policy decisions, lack of recognition of contributions, and poor opportunities for advancement [4]. Dr. Julie Sochalski, an expert in health policy who has conducted research on the shortage of nurses and consulted for the federal government about healthcare reform, argues that the current shortage cannot be remedied by enhanced recruitment alone. We must retain our best and brightest clinicians and it means that our work environments must be healed (J. Sochalski, personal communication, 2010).

Positive nurse–physician relationships coupled with adequate staffing and strong support from hospital administrators are associated with significantly lower rates of nurse burnout and with patients who were twice as likely to report higher levels of satisfaction with their care [5]. Conversely, in a study conducted in Switzerland, nurses caring for an average of eight patients daily felt that they needed to ration nursing care. Rationing was related to adverse patient outcomes such as medication errors, falls, avoidable critical incidents, and pressure

ulcers. Rationing included nurses' perceptions that they were unable to deliver needed nursing interventions such as feeding and hygiene, patient education and rehabilitation, monitoring, support and advocacy, and documentation of care and preventive functions such as appropriate hand washing. The Swiss investigators found that even low levels of rationing were associated with poor outcomes and yet they acknowledged that some rationing is inevitable. Further research is needed to identify a threshold in which truly unacceptable rationing occurs. It is likely that rationing of care, since it directly affects the patient, may be an important variable in understanding the influence of staffing and work environments on patient outcomes [6]. Burnout and dissatisfaction with rationing of care are clearly negative influences on a healthy work environment.

HEALTHY WORK ENVIRONMENT STANDARDS

In 2003, the Board of Directors of the American Association of Critical-Care Nurses (AACN) embarked on a strategic planning initiative to identify the three most pressing issues in which AACN's influence and voice could have the greatest impact on members. Consensus emerged that nurse staffing, healthy work environments, and end-of-life care were pivotal issues. Staffing and healthy work environments were seen as critical issues for nursing's largest specialty organization because of evidence that strong and supportive environments contribute to lower patient mortality rates [7]. Healthy work environments are those in which professionals work as team members, respect each other, and display caring for patients and families as well as each other. In these environments, effective collaboration provides opportunities for shared problem solving and emergence of shared mental models that support new solutions [2]. Professionals are empowered to practice according to the standards of their professions, including making decisions about their practice. They are led by leaders with the skills and power to design and implement a vision for superb practice. This was the vision that motivated the AACN Board of Directors to charge a work group, led by past president Connie Barden to develop healthy work environment standards [8]. These standards, listed in Table 206.1, were designed to give a strong message that immediate change in current practice settings was needed. Research identifying factors foundational to healthy work environments support AACN's decision to select these standards as the framework to drive widespread change.

TABLE 206.1

AACN STANDARDS FOR ESTABLISHING AND SUSTAINING HEALTHY WORK ENVIRONMENTS: A JOURNEY TO EXCELLENCE

Skilled Communication: Nurses must be as proficient in communication skills as they are in clinical skills
True Collaboration: Nurses must be relentless in pursuing and fostering true collaboration
Effective Decision Making: Nurses must be valued and committed partners in making policies, directing and evaluating clinical care, and leading organizational operations
Appropriate Staffing: Staffing must ensure effective match between patient needs and nurse competencies
Meaningful Recognition: Nurses must be recognized and should also recognize others for the value each brings to the work of the organization
Authentic Leadership: Nurse leaders must fully embrace the imperative of a healthy work environment, authentically live it, and engage others in its achievement

Adapted from American Association of Critical-Care Nurses: AACN Standards for establishing and sustaining healthy work environments: a journey to excellence. *Am J Crit Care* 14(3):187–197, 2005.

ENHANCING COMMUNICATION AND COLLABORATION: EFFECTIVE DECISION MAKING

There is evidence that nurses and physicians who work together differ significantly in their perceptions of collaborative decision making. In a large French study involving over 3,000 nurses and over 500 physicians, over 90% of the total sample agreed that decisions involving patients' end-of-life care should be made collaboratively. In practice, however, physicians were nearly twice as likely as nurses to report that nurses were involved in decision making (50% vs. 27%) and were significantly more satisfied with decision processes (73% vs. 33%, $p < 0.001$). These uneven perceptions were paralleled by strong differences in reports of physician consultation with nurses in the decision making process (79% vs. 31%, $p < 0.001$). Nurses were much more likely to feel that their presence in the meeting with the family was important. They valued being there more than the physicians valued their presence (56% vs. 36%, $p < 0.05$). The importance of these findings to clinical practice was evident in that significant linkages were found between satisfaction with decision making, perception of the unit's commitment to high ethical standards, and nurses' involvement in achieving these standards ($p < 0.0001$) [9]. Understanding that providers have disparate views of successful collaboration provides insight into potential root causes of communication problems both in day-to-day practice and when providers and patients face tough decisions. Efforts to achieve an ethical solution to practice dilemmas using processes that respect and value the input of the entire healthcare team are needed to achieve truly healthy work environments.

Effective communication has been shown to affect prevention of adverse outcomes. In particular, timeliness of nurse–physician communication was related to decreased incidence of pressure ulcers in a critical-care patient population, and conversely, when nurses perceived variability in communication with physicians, ventilator associated pneumonia (VAP) rates were higher [10]. Given the importance of preventing adverse events, it is reasonable to consider changes in care processes to foster clear and effective communication. System changes such as use of multidisciplinary rounds, appointment of a hospitalist medical director, and addition of a nurse practitioner (NP) to support the care interface between staff nurses and physicians are becoming more common, particularly in tertiary care hospitals. In a setting with these values in place, when care in that environment was compared with standard practice on a similar acute medical care unit, it was found that attending physicians and house staff perceived nurse collaboration to be significantly better but both the physicians and nurses rated collaboration with the NPs to be significantly better than with each other. No differences were found between nurses' perceived communication and collaboration with physicians on the model unit versus the standard practice unit. However, physicians on the model unit reported improved communication with each other. Improved patient outcomes included reduction in patient length of stay and care costs without reductions in quality of care or increased readmissions [11]. A possible explanation for the positive outcomes of physician/NP collaboration may lie in an appreciation of skills gained through NP versus MD education. It has been argued that NPs may be more adept at managing

patients through chronic care protocols in primary care. This is supported by their nursing background with its focus on patient education and use of communication skills [12]. Hence, the NP lives in both worlds and can easily translate and fill in gaps.

Why would physicians and nurses perceive care processes so differently? As was evident in Vazirani and colleagues' study [11], staff nurses may have difficulty being freed from direct care responsibilities to be able to participate in patient rounds or may be uncomfortable presenting their data and recommendations and thus avoid participation. Clear expectation for each provider's role in rounds, support for their participation through patient coverage, and providing adequate mentoring of young professionals in effective participation strategies are needed. Dialogue to ensure clarity about the characteristics of good collaboration and to develop respect and recognition of the value of each others' contributions are important steps in achieving benefits for patients and providers. Without this preparation, physicians may view improved collaboration to mean simply receiving accurate patient information and nurses following through on physician orders versus actual sharing in the decision making process. Addition of an NP to the team may serve as a bridge between nurses and physicians, improving the flow of information but may have the unintended effect of predisposing the nurses to communicate with the NP at times when they otherwise may call a physician [11].

Nurse–physician communication difficulty may have its roots in disparate educational systems. In their basic education, nurses are expected to present a broad, comprehensive picture of the patient's situation, in contrast to the targeted, specific problem focus that drives physician communication [13]. Nursing case summaries are graded highly if they thoroughly addressed the patient's physical health problems, including supporting pathophysiology, emotional and coping reactions, family and community support systems, and the interrelationships between all of these, resulting in a comprehensive nursing care plan that also integrates the nurse's support of the medical plan. Parsimonious, concise descriptions tend to be graded as missing key information and insights. Those training exercises, while designed to educate the nurses to view the patient holistically as a being with vast nursing needs beyond the medical illness, do not prepare them for a concise, problem-specific and action-driven health system, particularly as exists in critical-care settings. Thus, vastly different and ingrained way of thinking about patients' problems coupled with hierarchical power differentials can lead to pervasive dysfunctional norms of communication. Fear of reprisal or ridicule blocks interjection of critical information into the dialogue. Reliance on vague, imprecise communication styles may exclude critical information or urgency in message delivery. Leonard and colleagues [13] refer to this as the "hint and hope" model—one that holds a strong potential to harm patients.

Similarly, if a culture of perfection, personal failure, and blame exists rather than one of analysis of human and systems factors that contribute to errors, the tendency to bury errors and near misses rather than discuss them openly and correct root causes, further impede effective communication and harm patients [13]. Effective communication skills are needed. Given the authentic team leadership and implementation of skill building strategies, nurses can learn to participate effectively in interdisciplinary rounds, to summarize concisely changes in patients' conditions and to advocate for their needs, and to diffuse the inevitable conflicts that emerge among the healthcare team and with patients and families [14].

A widely used communication tool, SBAR (situation, background, assessment, recommendation) supports concise and organized communication between providers. It is a structure that guides a nurse's explanation of the situation, focusing on relevant background information, an assessment of what is happening and recommendations for corrective action. This technique has been criticized, however, for its failure to ensure that each provider fully understands the patient's problem and recommended action. Consequently, another tool gaining acceptance, STICC, adds a requirement for feedback and clarification of misunderstanding. With this tool, S describes the situation (Here's what I think we face), T is the task (This is what I think we should do), I refers to intent (This is why we should do it), C describes concern (What we should keep our eyes on), and C provides an opportunity to calibrate (Now let's talk; tell me what you don't understand, can't do, or if you see something I don't) [15]. Outcomes improve in settings in which nurses are empowered to state clearly that the patient requires immediate attention and can expect that this message will receive an immediate response, no matter the time of day or day of the week. While techniques such as SBAR and STICC improve the clarity of the message, the sense that "something isn't right" should be recognized as a call to action. Borrowing techniques in critical language from the airline industry such as the CUS system (I'm concerned, I'm uncomfortable, this is unsafe or I'm scared) provides a shorthand way of alerting colleagues that the problem is serious and demands attention. It is inevitable that false alarms will occur but a culture of effective communication and collaboration further supports strengthening nurses' assessment and communication skills [13].

STAFFING

An emerging body of research demonstrates strong connections between nurse staffing, particularly RN staffing, and patient outcomes. For surgical patients in acute care hospitals, increasing Registered Nurse (RN) care hours by 1 hour per day resulted in an 8.9% reduction in the patients' odds of developing pneumonia. The importance of the RN's role in care, as compared to less skilled nursing personnel, was further validated by a reduction in the risk of pneumonia by 9.5% when the proportion of RNs to overall nursing personnel increased by 10% [16]. Turnover of nursing staff has been shown to affect how a healthcare team learns from experiences with each other so that their abilities develop and they grow in behavioral skills and that, in turn, affects patient outcomes. Higher levels of workgroup learning were associated with higher patient satisfaction and fewer severe medication errors. Conversely, workgroup learning was found to be lower when turnover levels were moderate (3.31% to 4.5%) [17].

Evidence is also emerging that the educational level, skill set of the nurse, and quality of nurse–physician relationships make a difference. A 10% increase in the number of nurses prepared with a baccalaureate or higher degree resulted in a 5% decrease in both the likelihood that a surgical patient would die within 30 days of admission or that a failure to rescue event would occur [18]. These results occurred even after adjusting for patient characteristics such as comorbid conditions, hospital characteristics such as size, teaching status, and technology level, nurse staffing and experience, and the board certification status of the surgeon. Similarly, substituting unlicensed aids for RNs has been shown to reduce quality outcomes in a large study (18,142 patients) of patients with common cardiovascular and pulmonary diagnoses. The largest part of the variance in 30-day mortality rate was attributed to patient age and illnesses (44.2%). However, hospital and nursing factors accounted for an additional 36.9% of the variance. Lower 30-day patient mortality rate was found in settings with a higher proportion of baccalaureate nurses (OR, 0.81; 95% CI [0.68, 0.96]), presence of more RNs versus less skilled nursing personnel (OR, 0.83; 95% CI [0.73, 0.96]), and healthy nurse–physician relationships (OR, 0.74; 95% CI [0.60, 0.91]).

The use of temporary nurses was associated with a higher 30-day mortality rate (OR, 1.26; 95% CI [1.09, 1.47]) [19].

Nurses, however, perceive that staffing to deliver quality care involves more than simple nurse-to-patient ratios. In a study based on interviews conducted with 279 nurses from 14 Magnet Hospitals, nurses perceived staffing to be adequate when all providers worked as members of a team, collaboration was strong, and nurses possessed the knowledge, experience, and skills to meet patient needs. Empowerment to make autonomous clinical decision and control of their practice environment were crucial factors as were support strategies such as computerized documentation, order entry systems, and well trained, motivated, assistive personnel and support services. Patient acuity influenced staffing perceptions but these nurses perceived that high patient acuity was best handled when other positive work environment characteristics were present. Nurses valued administrators' recognition of the need to factor patient acuity into staffing allocations [20]. In a study of nearly 8,600 Canadian nurses, an analysis of nurses' perceptions about their work environment found a direct causal relationship between poor staffing and nurses' emotional burnout, and a direct positive relationship between the presence of a nursing model of care, one that values nurses' personal and professional ideals, and personal accomplishments [21].

The notion that perceived staffing adequacy is not as simple as nurse–patient ratios was addressed in a significant way by AACN and the AACN Certification Corporation when they charged a workgroup with developing and refining a new

TABLE 206.2

AACN'S SYNERGY MODEL FOR CLINICAL EXCELLENCE: PATIENT CHARACTERISTICS

- **Resiliency:** The patient's capacity to rebound or return to function using compensatory physiological and other coping mechanisms; a history of adapting to significant stressors; reserve capacity
- **Vulnerability:** Degree of susceptibility to real or potential stressors; affected by physiological capacity, coping ability, pre-illness health status; the person's ability to protect themselves from threats
- **Stability:** Capacity to maintain a steady state, maintain equilibrium; influenced by responsiveness to therapies
- **Complexity**: Interconnectedness of two or more systems; can be physiological, psychological, family interactions or environmental impact; with greater numbers of systems affected, complexity increases
- **Resource Availability**: Supports available to the patient by the family, community, and the patient himself/herself; resources are broadly defined: physical, emotional, fiscal, social, personal; in general, more resources are linked to better outcomes
- **Participation in Care**: Engagement by the patient and family in care processes; influenced by educational levels/health literacy, cultural background and resources
- **Participation in Decision Making:** Ability to comprehend and act on information and to contribute to decisions; influenced by cultural background, degree of physiologic function, beliefs and values
- **Predictability**: Accuracy in anticipating responses and course of illness; facilitates use of diagnostic indices and evidence-based pathways to plan care

Adapted from Hardin S, Kaplow R: *Synergy for Clinical Excellence. The AACN Synergy Model for Patient Care*. Sudbury, MA, Jones and Bartlett Publishers, 2005, pp 3–54.

TABLE 206.3

AACN'S SYNERGY MODEL FOR CLINICAL EXCELLENCE: NURSE COMPETENCIES

- **Clinical Judgment:** Nursing skill, clinical reasoning, and critical thinking abilities developed over time through education, practice, and attention to evidence-based care; ability to integrate patient-specific knowledge into care planning and delivery
- **Advocacy:** Serve as a moral agent, one who intervenes to support another who cannot voice her/his own rights and needs; helps to resolve ethical conflicts and clinical problems for patients and families
- **Caring Practices:** A large collection of nursing practices that provide a therapeutic, supportive, and compassionate environment that promotes healing and prevents unnecessary suffering; applies to patients, families, and staff
- **Collaboration:** Cooperative engagement among all members of healthcare team, along with patients and families to achieve optimal and realistic patient goals
- **Systems Thinking:** Ability to see the real causes of problems; knowledge and skills to manage the environment and resources for the betterment of the patient, family, and health care team, within and across health and non-healthcare systems
- **Response to Diversity:** Recognition, appreciation, and incorporation of differences among racial, ethnic, marginal, and vulnerable populations to support individuality, cultural attributes, spirituality, family, and lifestyle preferences into the provision of care.
- **Clinical Inquiry:** Persistent process of questioning and evaluating practice to ensure that practice is informed by current research and experiential learning
- **Facilitator of Learning:** Recognition of patient and family needs for knowledge and skill development and use of standardized and patient appropriate materials and creative strategies to ensure that patients and families are prepared to handle their healthcare needs; valuing and promoting life-long learning among all members of the team.

Adapted from Hardin S, Kaplow R: *Synergy for Clinical Excellence. The AACN Synergy Model for Patient Care*. Sudbury, MA, Jones and Bartlett Publishers, 2005, pp 57–107.

paradigm for clinical practice. Initially designed as a framework to guide development of a conceptually redefined certification examination, the model became a driving force to articulate nurses' contribution in achieving AACN's vision—*a healthcare system driven by the needs of patients and families where acute and critical-care nurses make their optimal contribution* [22]. The Synergy Model for Clinical Excellence identifies patient characteristics and nurse competencies that, when matched appropriately, enable patient outcomes to be optimized [23]. Table 206.2 describes the patient characteristics and Table 206.3 identifies the competencies of the nurses caring for these patients.

RECOGNIZED POSITIVE WORK ENVIRONMENTS: MAGNET HOSPITALS AND BEACON UNITS

During the 1980s, nursing administrators noted that some hospitals continued to maintain adequate staffing even during nursing shortages. Subsequent research identified the positive practice environment characteristics of these hospitals and the

term "Magnet" was applied to them since they served as a magnet for nurses. The knowledge gained from this research was used by the American Nurses Association and its accrediting arm, the American Nurses Credentialing Center (ANCC), to develop a Magnet Recognition program to identify those hospitals with the quality indicators and standards of care that result in excellence in patient care and an exemplary practice environment for nurses. Of the prestigious *U.S. News & World Report* Honor Roll of top hospitals, 71% of medical centers and 90% of the Children's Hospitals achieving that designation are Magnet organizations [24].

In 2003, AACN launched the Beacon Award for Critical-Care Excellence. This highly competitive award recognizes individual critical care and progressive care units whose staff has achieved high levels of quality patient and family care and excellent care outcomes within a healthy work environment. The award recognizes outstanding outcomes in recruiting and retaining a staff that values ongoing education and training to sustain competent practice, research and evidence-based practice, strong leadership and commitment to organizational ethics, and a sustained healing environment [25]. While nurses tend to lead the movement to attain Beacon status, this honor cannot be achieved or sustained without significant interdisciplinary collaboration and authentic leadership to transform the practice environment.

The benefits of a healthy work environment and factors associated with sustaining it can be understood by examining work environment research conducted in Magnet institutions. For example, when work environment characteristics of 23 Magnet institutions were compared with 156 non-Magnet hospitals, Magnet designation was associated with significantly more decentralized decision making involving nurses, collegial nurse/physician relationships, adequate staffing, presence of nurse managers with good leadership skills, and a preceptor program for newly hired RNs. Without Magnet designation, only 17.3% of the hospitals scored well on practice environment measures and all scored lower on all characteristics than the ANCC Magnet hospitals [26]. Similarly, a survey of over 2300 nurses from 110 ICUs in 68 hospitals revealed that nurses in Magnet hospitals perceived their work environment to be significantly better than those in non-Magnet facilities [27].

In a study of over 4,000 nurses, Ulrich and colleagues [25] examined perceptions of work environments within agencies that had Magnet or Beacon status, were actively pursuing either status, or had neither status. Nurses in Magnet or Beacon agencies had significantly more positive appraisals of the work environment, greater current job satisfaction, a higher rated skill set of the nursing leadership team, and improved quality of care compared with non–Magnet/ Beacon agencies. They also rated quality of interdisciplinary team communication and collaboration more positively, as well as respect for RNs, organizational support for education and certification, and nursing career satisfaction. Shared governance structures were significantly more likely to be in place in Magnet or Beacon organizations. In many of the parameters measured, units and organizations on the journey to Magnet or Beacon fared significantly better than those groups not pursuing that designation [25].

Insight into factors that staff nurses, physicians, and nurse managers perceive to be most important in the work place may help colleagues understand differences in expectations and emphasis in effort. In a survey of all three groups working together in Magnet institutions, Schmalenberg and colleagues [20] found that physicians overwhelmingly viewed a competent nurse as a colleague who was able to make timely, correct, and independent decisions to support patients. These physicians reported that they rely on nurses who can quickly discern what patients need and implement the required care, particularly when physicians were unable to be physically present.

TABLE 206.4

SPECIFIC STRATEGIES TO IMPLEMENT HEALTHY WORK ENVIRONMENTS

1. Empower nurses to control practice through strong physician and team collaborative decision making and active participation in interdisciplinary rounds; teamwork becomes a core value.
2. Shared governance models included members from multiple departments and disciplines resulting in an "integrated" model that is far more efficient and empowering than single discipline "silo" governance models (p. 82).
3. Staffing structures that allow nurses the time to attend rounds and governance meetings. Governance structures that support nurses' input into decisions by administrators, physicians, and others.
4. Groups own the outcomes of decisions and care improvement efforts; a culture exists that appreciates individual and group contributions
5. Quality patient care is based on the best scientific evidence and is morally and ethically congruent with the patient's wishes and professional standards.
6. Safe care is the minimum but goals demanded excellent, high quality patient/family centered care.
7. Competence, ongoing education, personal accountability for evidence-based practice, and certification were valued and expected.
8. Camaraderie and a family orientation among team members resulted in a nurturing work environment where expression of concerns and feelings was the norm. Team members supported and filled in for each other without grumbling.
9. Respect, trust, and treating each other as equals and with dignity were valued. The same principles applied to interactions with patients and families.
10. Honesty and integrity as core values were reflected in communication; team members are reluctant to place blame, seeking instead root causes of problems. Willingness to acknowledge mistakes and short comings is valued.
11. Patient advocacy and clinical autonomy are supported by appropriate surveillance to prevent complications or rescue patients and a passion to get patients what they need.
12. Stewardship means that the team values the patient's and each other's time and energy; appropriately uses and conserves resources and delivers quality outcomes.
13. Active transmission of core values and unit norms to new members of the team happens because managers and team members develop and implement a conscious plan to ensure that the values and norms become entrenched in the culture of the team.

Adapted from Kramer M, Schmalenberg C, Maguire P, et al: Walk the talk: promoting control of nursing practice and a patient-centered culture. *Critical Care Nurse* 29(3):77–93, 2009.

These comments clearly demonstrated that competent nurses earned the trust and respect of physicians [14].

Nurse manager expectations were similar in that they valued the vigilance, advocacy, and persistence of competent nurses. While correctly interpreting what is happening and acting on it was critical in their view, they also valued nurses who demonstrated commitment to ongoing competence through education. The managers expected that nurses request increasingly challenging assignments, incorporate the latest evidence-based practice standards into care, and manage both complexity and volume of care responsibilities. Organizational skills of priority setting and multitasking are needed to manage the demands of busy units, but competent care demands complex thought processes and decision making skills while retaining empathy and concern for the individual patient [14]. Thus, managers' view of competence is much broader than that reported by physicians in this study. While physicians and staff nurses agreed on the importance of clinical knowledge and decision making and physicians welcomed and expected the input of competent nurses, they may have failed to comprehend the full range of nursing duties, particularly with a full caseload of acute and critically ill patients. Hence, the importance that nurses and nurse managers place on multitasking is understandable [14]. These findings support the notion that healthcare today is characterized by "complexity compression," a term that describes the challenges inherent in taking on additional responsibilities while simultaneously providing highly complex care in a condensed time frame [28]. For today's work environments to become healthy, recognizing that complexity compression affects all providers is a critical step. As our reliance on each others' expertise grows, our appreciation for the demands on each other and our support for each other must grow as well. Specific characteristics demonstrating achievement of a healthy work environment are described in Table 206.4.

TRANSFORMING WORK PLACES: AUTHENTIC LEADERSHIP

Achieving and sustaining the change described in these studies requires leaders with the skills to build teams and motivate staff to develop a broad set of competencies in communication, collaboration, decision making, as well as evidence-based practice. Individual as well as team competencies are needed to transform work places and sustain positive change. One strategy that was found to increase significantly collaborative communication, problem solving, and conflict management skills was a 24-hour program using a modular format that offered leadership and communication training to physician and nurse leaders in an organization. Strong engagement was reflected in attendance rates of over 90% of the sessions and positive evaluations about the usefulness of the learning. While this study involved a small sample, it demonstrates that investing in joint physician–nurse leadership competency development is effective [29].

Efforts to create healthy work environments through systems improvements and enhanced skills in communication, collaboration, and leadership are likely to have additional payoff in terms of patient outcomes and satisfaction. To turn our current silo-driven, fragmented health systems into centers of patient-focused care, we must ensure that sustained commitment to collaborative care is based on effective communication and is led by authentic leaders [30].

CONCLUSIONS AND NEXT STEPS

Let's return to where we began—the job interview scenario. Thriving in today's difficult practice world demands that we acquire a strong base in the evidence supporting clinical care. Colleagues who share that commitment will contribute to our growth in knowledge and clinical decision-making skills. Evidence is also growing that patient outcomes are not controlled only by the clinical decisions we make but by the environment where those decisions are implemented. Healthy workplaces promote collaborative decision making, leading to better informed decisions and avoidance of incomplete or inaccurate information that contributes to adverse events and poor outcomes. Therefore, gather as much information as you can about the practice climate, interprofessional relationships, and skills of the leadership team. Ask to speak with members of the disciplines you will be practicing with to understand the real level of collaboration that exists. Interview the managers and leaders you will be working with to ascertain their commitment to achieving a work environment where you will make your optimum contribution and thrive. Finally, be a force for a positive environment that supports each other as well as patients and families. The factors listed in Table 206.4 provide a start. We all have a stake in the process and the outcomes.

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CHAPTER 207 ■ ICU NURSING IN THE TELEMEDICINE AGE

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INTRODUCTION

In the 1999 publication by the Institute of Medicine, *To Err Is Human*, the authors painted a grim picture of medical errors in hospitalized patients [1]. The report stated tens of thousands of patients each year suffer a preventable medical error. Errors can lead to death, physical impairment, increased length of stay, and cost increases amounting to billions of dollars. The Institute of Medicine (IOM) estimated that almost 100,000 American patients die yearly from medical errors making it the eighth leading cause of death in the United States.

Historically, Intensive Care Units (ICUs) are major sites for medical errors and complications. Patient safety experts cite outmoded systems of work as the reason for many of healthcare's errors and quality problems [2]. It is believed that redesigned systems will yield safer, better care. According to the Leapfrog Group, a healthcare advisory board for Fortune 500 companies [3], more than four million patients are admitted to the ICUs and approximately 500,000 die annually. They estimated that providing a dedicated, intensivist-based care model could save between 50,000 and 100,000 lives annually [4] and that mortality could be reduced by 15% to 20%.

Modern ICUs are complex and prone to errors [5]. In 1999, Doering described what she termed as threats to effective collaboration in the critical care setting [6]. These threats included the complexity of the environment and the increasing workloads of staff at the bedside. She suggested that the process of effective collaboration required a commitment of administrators and staff alike when both are facing competition for scarce resources. Effective communication and collaboration required time and nurturing from all involved. It should be built on a concept of trust and could not be rushed and is often the first thing to be omitted when outside forces pull caregivers in different directions.

AGING WORKFORCE

Long lengths of stay, higher rates of infection, and failure to rescue are patient care outcomes that have been linked with nurse staffing levels [7]. Concerns related to the implications of a projected nursing shortage has influenced interest in how staffing mix as well as sheer loss of numbers of critical care nurses could lead to an increase in errors in patient care. This led to the passing of the Nurse Reinvestment Act (NRA), Public Law 107–205 in 2002 by Congress. This legislation was aimed at stimulating the growth of the nursing profession [8].

The composition of the registered nurses (RNs) workforce was predicted to shift to the largest group of RNs being in the 50- to 60-year-old age group by 2010 and according to a recent study by Auerbach et al., RNs in their 50s will outnumber all other age groups in this profession by 2012 [9]. The demand for RNs is predicted to accelerate at the same time as the nation's eighty million baby boomers begin to reach the age of 65. By 2020, the gap between supply and demand of RNs is estimated at over 400,000 [10].

Although some progress has been made in recruitment and retention of nurses, the future projections still fall short of the goal of maintaining a supply and demand balance for this vital workforce. Discovering more innovative solutions to leverage nursing expertise and practice is needed. The Sixth report by the National Advisory Council on Nurse Education and Practice (NACNEP) recommended the use of simulation-based education as well as utilization of interactive Internet-based learning programs to enhance effectiveness of nursing education and critical thinking skills. Strategic use of technology to not replace the nursing workforce but to enhance skill mix and staffing as well as to prepare and support the novice nurse was also recommended [11]. Leveraging nursing practice and expertise through the use of technology is the essence of telenursing.

A task force was commissioned by the Robert Wood Johnson Foundation to publish a white paper in 2006 to identify

strategies and opportunities for retaining the experienced nursing workforce. This paper examined the effects of loss of knowledge that occurs when older experienced nurses leave the profession [12]. Leading experts are convinced that organizations suffer detrimental effects on productivity and performance with loss of older employees. Shifting the ratio of experienced nurses to less experienced nurses will have serious implications on quality and safety of patient care according to national experts [12]. If the emerging role development of the telemedicine team is fostered by internal driving forces of clinical competence, independent decision making, and strong interpersonal skills, then can telemedicine enable a new care delivery model that embraces empowerment through leveraging of critical resources?

What happens to nursing knowledge, if as projected, large numbers of experienced nurses leave the field all at once? Bleich et al. warns that the implications of loss of knowledge will be devastating to not only performance and productivity but the shift from "experienced to less experienced nurses will have serious implications for quality and safety of patient care" [13]. The authors go on to explain that more than just "rudimentary skills and routine know-how about common processes" are required, these nurses also have "deep-smarts," a "tacit knowledge" that is difficult but not impossible to articulate into formal language. It is a knowledge that is gained through the maturation process of being a nurse; a synthesis of learned knowledge, deep insight, and intuition that allows the experienced nurse to incorporate multiple assessment variables rapidly into an assessment and a plan of care. It is the "state of knowing" that could be lost as nurses leave the profession if we do not find innovative and creative solutions to maintain and leverage it.

IS TELEMEDICINE THE ANSWER?

According to leading experts, telemedicine may be leveraged to support a multidisciplinary intensivist-led team and incorporates re-engineering of workflow processes, outcome measurement, collaboration and professional role development to facilitate efforts to change behavior for improved patient quality [14]. Telemedicine is defined as the transmission of electronic data from one location to another to allow for remote evaluation of the data by a medical professional [15–17]. Data may include pictures, EKGs, radiology studies, or audio–video feeds. The remote medical professional then communicates back to the sending facility with an opinion using one of several means, including fax, audio, video, or other electronic means.

The concept of telemedicine has been around for several decades. Telemedicine in its current form can be found in the literature as far back as the 1950s [15]. The National Aeronautics and Space Administration monitored astronauts' heart rate and respirations while in space from a remote location or during test runs on the earth. NASA continued to monitor astronauts and to develop computer software over the ensuing years [15]. Several projects were funded by government agencies in the 1960s, 1970s, and 1980s to bring medical care to remote or hard to reach locations both nationally and internationally, often using microwave audio and video communication. Most of these early projects could not be sustained due primarily to the prohibitive cost of the microwave communication technology [16].

During the 1990s, the availability and transmission of digital radiological studies allowed the efficient reading of images remotely, allowing a single radiologist from a different location to interpret studies when an on-site radiologist was not available. Another use that gained favor around the same time was the use of psychiatric staff doing remote evaluations. Telemedicine has also allowed neurologists to remotely review studies and allow for real-time decision making in the treatment of acute stroke care [17]. This along with changes to the laws required for consults to allow for neurologists to bill for their remote services has greatly enhanced the care of these patients.

Today telemedicine is a significant component of the Department of Veterans Affairs strategic plan to care for veterans [18]. According to the American Psychiatric Association, "Telepsychiatry is currently one of the most effective ways to increase access to psychiatric care for individuals living in underserved areas" [19]. The Department of Health and Human Services, Health Resources and Services Administration (HRSA), supports the use of telehealth to meet the needs of underserved people [20].

Over the past 10 years the advancement of computer systems of relatively low cost and of faster transmission has greatly enhanced what data can be viewed from a remote location. The advent of clinical documentation systems at the bedside have further made the data readily available using electronic means. Over the past 35 years, research scientists have worked to develop computer systems to assist clinicians in making decisions related to patient care [21]. This coupled with high-resolution audio–video technologies have led to the emergence of telemedicine in the intensive care unit or tele-ICU care.

TELE-ICU STAFFING PATTERNS

A modern tele-ICU center is typically staffed by both clinical and nonclinical members. The fundamental component to the remote clinical team includes experienced critical care nurses and physicians specializing in Critical Care Medicine. Other board certified specialty physicians such as cardiothoracic, pulmonary medicine, cardiology, and trauma/surgery may serve as the tele-ICU physician. Affiliate practitioners such as Nurse Practitioners and Pharmacists are adjunctive team members in some tele-ICUs to leverage resources in patient monitoring, management, and performance improvement. Operational processes are supported by nonclinical staff in the tele-ICU center through timely, current data entry and by facilitation of communication between remote and onsite teams.

The number of clinical and nonclinical staff required for each program is dependent upon the volume of monitored beds and the off-site team's level of involvement with the bedside. At least one physician along with several nurses and nonclinical support consist of the core team members each shift. An additional physician or mid-level practitioner such as an advanced practice nurse may be needed to meet the demands of monitoring larger patient volumes. The tele-ICU care team composition is dependent on the type of service provided. There are specialty physicians providing consultative care models using telemedicine technology to support the care of critically ill patients. Some of these care modalities use telenursing support in their programs.

Tele-ICU staffing is impacted by several factors including the ratio of patients monitored per tele-ICU nurse. Typically, one tele-ICU nurse monitors approximately 35 to 50 patients. The ratio affects the number of nurses required each shift to staff the tele-ICU.

One consideration of staffing is the degree of integration and effort needed by the tele-ICU nurse to maintain timely data for monitoring and interventional purposes. Another consideration in managing this many patients is the degree of electronic documentation performed at the bedside versus the remote site. Fragmentation of documentation (paper, electronic, combination) impacts monitoring abilities of the tele-ICU nurse and demands greater oversight to maintain accuracy of data.

TELE-ICU NURSING

The ICU nurse is a key leader to clinical transformation and the re-engineering of care processes. Therefore, it would follow that the tele-ICU nurse would and should be an integral part of the tele-ICU team. What makes the tele-ICU nurse think differently than the bedside ICU nurse? How does the tele-ICU nurse use or draw upon innate cognitive abilities when processing information? Drawing from previous experience, training and knowledge the expert critical care nurse uses tacit knowledge to synthesize complex physiological information and care modalities into nursing diagnoses and recommendations for optimizing patient care. Information technologies (ITs) allow nurses to not only view information remotely but to observe pertinent data in an organized, real-time manner enhance the efficiency in which clinicians can amalgamate information.

TRANSITION FROM THE BEDSIDE

The tele-ICU nurse requires a transitioning process to fulfill role development. The transitioning period or role development may last several months past orientation. A fundamental aspect of this period is learning new responsibilities as a tele-ICU nurse versus an ICU nurse. Role development encompasses expanded functions as mentor, preceptor, educator, leader, and program advocacy. Unlike bedside care, the tele-ICU nurse must learn to transition from hands-on care to technology-driven care.

Conceptual development is important to understanding role transition of the tele-ICU nurse. Discussion of conceptual development of the tele-ICU nurse is limited to absent in the literature. Understanding what makes the tele-ICU nurse transition into an emerging new breed of caregiver is important to the future of nursing practice. A paradigm shift occurs in care delivery once the bedside ICU nurse transitions into a tele-ICU nurse. The shift in traditional care delivery of one to three ICU patients is now dozens of patients per shift. How does the tele-ICU nurse begin to conceptualize and synthesize from managing individual patients to whole populations of patients occur? Benner [22] identifies five stages of nursing development and the teaching/learning needs at each stage. These stages are congruent with the professional role development and transition period of the tele-ICU nurse. Unlike a new graduate nurse at the novice stage of professional bedside practice, the tele-ICU nurse possesses clinical experience but is new to the emerging role of the remote environment as well as to using IT to drive decision making and assessment practices. All nurses transition to some degree through these five stages of development regardless of their specialty area. The time spent in each developmental stage will vary with each nurse and the ability to adapt to the complexity of the new role.

The case could be made that these expert nurses should be physically present at the bedside caring for complex patients and providing face to face mentorship of novice nurses. How could taking more nursing expertise away from the bedside actually serve to enhance staff mix? Because of nurse supply and demand trends and predictions, finding alternative ways to leverage nursing expertise across the over 6,000 ICU in the nation will take a creative and innovative approach [23].

Expertise and knowledge working in isolation from caring can hinder execution of high level nurse practice. Therefore, it is imperative to include a balance of knowledge and caring in the development of the emerging discipline of virtual or tele-ICU nursing. Dr. Jean Watson's Theory of Human Caring contain 10 factors that are described by her as "those aspects of nursing that actually potentiate therapeutic healing processes and relationships; they affect the one caring and the one-being-cared-for" [24]. She describes the soul or spirit within human beings as "greater than the physical, mental, and emotional existence of a person at any given point in time." According to Watson, this inner spirit allows each individual to achieve a "higher degree of consciousness, an inner strength, and a power that can expand human capacities." The virtual nurse should possess a deep-rooted attribute of caring that extends to not only patients but also to the care providers at the bedside.

TELE-ICU COLLABORATION

The tele-ICU nurse needs to balance caring with power to meet the needs of the patient–family unit through negotiation and advocacy. The concept of power is frequently associated with negative connotations such as restricting freedom, authoritative leadership, and hierarchical status [25]. Power also is referenced to coercion and domination of others. Leaders may display various forms of power or a lack of power depending on the situation and degree of empowerment. Legitimate power is when one person relinquishing power to another individual. This power is associated with action and expertise. Power can be connected with knowledge, coercion or conditioned.

The empowered tele-ICU nurse exhibits effectual use of clinical knowledge and innovative technology. Virtual rounding is an example of empowerment and is a principle mechanism to immediately serve as a clinical resource for assessment, intervention, or mentoring. Nurses should conduct virtual patient and environmental rounds proactively to assess for potential sources of complications, errors and interventional effectiveness. Understanding the concepts of social presence can effectuate acceptance from caregivers at the bedside and mitigate interaction issues related to critical missing communication cues.

Empowerment inherent in organizations where individuals are encouraged to assume responsibility and act in line with organizational goals is an approach that allows staff to retain control over their work, where responsibility is delegated within the hierarchy and resources are readily available [26,27]. Hence, organizational development for a tele-ICU service should begin with a vision and strategy that empowers the remote team to work toward the best care practices within an integrated team model. If this is not present then virtual teams will struggle against entrenched loyalties and hierarchical power structures that are prohibitive to safe and collaborative patient care. Some examples of integrated team approaches with a tele-ICU team are the following:

- Decreased ventilator days [28])
- Implementation of evidence-based best practice strategies at system levels [29,30]
- Ability to provide real-time feedback or reports to guide clinician practice
- Improved compliance to best practice standards [31,32]
- Increased cost effectiveness of critical care
- Prevention of cardiac arrest and complication prevention/management [33–36]

The virtual presence of the tele-ICU nurse may further complicates effective communication due to the lack of direct person to person contact and inability to read the body language. For decades, the healthcare industry has known that ineffective communication has been a significant factor in adverse events in hospitals and in critical care. Inadequate communication was cited as one of the main findings of the 1999 IOM *To Err Is Human* publication [1]. A 2003 study examined the attitudes of critical care nurses and physicians regarding collaboration and teamwork [37]. The results described that physicians predominantly found collaboration to be satisfactory yet the nursing staff interviewed found collaboration lacking. It is thought that communication and collaboration throughout critical care among caregivers is not what it should be [38]. This

is important to keep in mind from a tele-ICU perspective as the camera and microphone may be viewed as intrusive. We are reminded of this in George Orwell's 1949 novel "1984" [39]. Written at the end of World War II, it described a fictional society run by The Party, and it's affect on the main character, Winston Smith. In the novel, all thoughts and actions are controlled by the party, through the use of spies, cameras, and microphones. The controlling Party, and its leader, Big Brother, are attempting to control everything in the people's lives, from where they work to how they think. This "1984" mentality of technology connecting everyone in the world could contribute to a reluctance of care providers and consumers in embracing telemedicine as sound method of care delivery. Understanding this mind-set is important as telemedicine care providers address the communication and collaboration barriers that can surface when using technology-enhanced care modalities.

The tele-ICU nurse is in a unique position to view variation or gaps in care across and within health systems. As the tele-ICU nurse finds these opportunities for improvement this along with Appreciative Intelligence (AI) creates "survival anxiety" which can influence or prompt change to occur [40]. This leads to unfreezing of prior perceptions of care delivery and with AI, tele-ICU nurses can then reframe situations for better negotiating or problem solving in more creative ways. They can use concepts of AI to enhance critical thinking and drive interventions in order to achieve patient safety goals. For example, the tele-ICU nurse has the potential to view continuous vital sign trending. The bedside vital sign data is processed through decision support software that identifies early trends in deterioration. When a vital sign alert is triggered the tele-ICU nurse evaluates the alert for potential patient deterioration, using an audio–video assessment, review of laboratory values, and other pertinent clinical data to assist in the critical thinking and assessment processes. The tele-ICU nurse rapidly processes these data using tacit knowledge which leads to decision making related to evidence-based practice.

COMPUTER-ENHANCED CARE

Social presence (SP) using computer-mediated communication (CMC) has been studied in education disciplines [41–43] and its learnings can be applied to the telemedicine arena. Communication mediums can determine how well people communicate but that individual perceptions often have a powerful influence on acceptance of these mediums. SP has been described as the state of being "real" in mediated communication and is based in telecommunication literature. Social presence relates to how a person is perceived as being real and being there or present in communication [42].

The aspects of SP influence how well communication occurs. Although the degree of saliency and the quality of the social medium can assist in influencing satisfaction of users in using technology as a vehicle of communication, individual perspectives have been shown to be a powerful dynamic [43]. Factors that influence the degree of social presence are: verbal or nonverbal cues, physical proximity, formality of dress, facial expressions, eye contact, humor, and personal topics of conversation. CMC is considered low in the order of social presence [44]. Given previous statistics that highlight the role of communication in errors that harm patients, understanding the impact of modes of communication is important to this discussion. Tele-ICU nurses should receive advanced training in communication techniques and nursing leadership should design communication algorithms that enhance collaboration and mitigate negative perceptions. Further research is needed in the area of telenursing and social presence.

Since the tele-ICU nurse can manage 35 to 50 patients per shift, thoughtful strategies must be employed to accomplish efficient, comprehensive rounding. Studer, a nationally recognized healthcare management thought leader identified nine steps to standardize rounding [45]. These nine steps are applicable in various settings where rounding is present.

1. Give staff a heads-up. The tele-ICU nurse should inform the bedside caregivers of their presence and purpose for rounding.
2. Prepare a scouting report. Understand specific issues or situations within each unit that may impact rounding such as staffing constraints, new nurses.
3. Make a personal connection. Identify a common connection with bedside caregivers to facilitate compassion and genuine personal concern.
4. Identify an issue or concern raised on a previous rounding episode. Demonstrates your follow through to resolve an issue or problem.
5. Remember five questions framed in a positive manner. Script five basic questions that are communicated in a positive and inviting approach for rounding purposes.
6. When an individual identifies a problem, assure him or her that you will do the best to resolve their concern(s). Develops the foundation for open and trusted relationships.
7. Record issues that arise in a rounding log. This will allow for accurate accountability of issues and needs of the bedside caregivers or patients.
8. Recognize and reward those who are identified a high performers. Extending words of thanks for superior work and positive interactions develops strong relationships.
9. Repeat process. The tele-ICU nurse gains repeated experience with rounding since this is an essential function of their role.

TELEMEDICINE AND EVIDENCED-BASED PRACTICE

An expert committee formed by the IOM found that "current care is insufficiently reliable in its use of the best science and best-known practices because it lacks IT systems that put that knowledge at the point of use and because it honors and protects unscientific variations in care based on local habits, unquestioned forms of autonomy, and insufficient curiosity" [46]. According to leading nursing experts the acquisition and implementation of evidence-based practice is lacking in nursing practice [47]. Data also suggests that social interaction and experience are the two most utilized sources of practice knowledge for nurses [48]. Nurses in the virtual environment should maintain a high level of competency through attainment of advance certifications in critical care. Given this, the tele-ICU nurse has a unique opportunity to maintain and disseminate a high level of evidence-based practice knowledge.

CONCLUSION

As discussed previously, the expert nurse can rapidly put together the whole patient picture integrating the patient's needs into timely and appropriate nursing interventions while others may be focused on the next task or a technical skill [49]. This ability to synthesize knowledge into appropriate decision-making skills can then facilitate effective support to the bedside nurse practice. Nurses make hundreds of decisions a day when caring for patients [50]. The tele-ICU nurse can serve as not only a sounding board for bedside nurses as they make these decisions they can use influence and negotiating skills to facilitate evidence-based care practices. Within this context the virtual clinicians function autonomously yet collaboratively with bedside caregivers in clinical decision-making. The autonomy

and independence of the virtual team is cultivated from years of professional experiences, personal attributes, hardiness, and exceptional tacit knowledge synthesis skills. In this virtual environment, nurses and physicians are challenged differently than at the bedside. Monitoring patient data and intervening without physical presence demand skillful communication and expertise in critical care.

Leveraging scarce critical care nursing expertise is just one of the benefits of tele-ICU care models. An expert nursing team can coach and mentor novice ICU nurses remotely, reinforcing care practices, assisting in establishing patient goals, and enhancing critical thinking and assessment skills. Experience is a prerequisite for becoming an expert, according to research that focused on critical care nurses and the learning process [51]. Experts have the ability to go beyond the tasks to read and respond to the global needs of the patient. This allows for the ability to avert potential catastrophe or "failure to rescue" [49,51]. Most sites report that nurses working in a tele-ICU have on average 10 to 15 years of experience in various fields of critical care nursing.

Multidisciplinary integration of the tele-ICU technology and care delivery method through empowerment contributes to organizational acceptance and utilization [52]. Widespread integration with nurses, physicians, respiratory therapists, dieticians, physical medicine, and other care givers will leverage clinical and technical expertise. Data transparency can be enhanced across disciplines with immediate availability of electronic clinical documentation tools within software applications.

Using standardized reporting metrics to evaluate severity adjusted mortality and length of stay as well as compliance with best practice standards is a benefit to centralized data collection. Quality assurance/improvement oversight can be enhanced and efficiency improved with technological tools and tele-ICU processes [53]. This can lead to development of system wide clinical risk reduction strategies that can in turn improve patient safety and quality. Tele-ICU systems allow providers to extract reports from the software application in real-time to evaluate and intervene on patients at multiple intervals each day.

Robust health IT systems employ clinical decision support tools to prompt the clinician to institute evidence-based best practices at the point of care. These systems can provide real-time feedback and reports to alert the physician/nurse to any gaps in care that need to be filled. These "smart" systems coupled with collaboration between on-site and tele-ICU teams empower clinicians to implement best care processes effectively and consistently [54,55].

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SECTION XIX ■ CONTEMPORARY CHALLENGES IN THE INTENSIVE CARE UNIT

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CHAPTER 208 ■ ICU ORGANIZATION AND MANAGEMENT

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INTRODUCTION

Organization is the act of assembling elements into an orderly, functional whole. Management is the ongoing revision and renovation of that careful assembly to cope with change. The concept of "bedside management" is familiar to clinicians who titrate vasopressors or adjust ventilator settings; intensive care unit (ICU) management is itself a form of titration and continuous adjustment. ICU management extends beyond simply implementing policies and procedures, organizing service and teaching rounds, preparing budgets, and complying with regulations. The successful ICU manager must also innovate and facilitate change. Creativity is important, but perseverance may be more essential because of the ways a typical organization will resist change. Knowing how to navigate the obvious and subtle impediments to change is a key skill for the ICU manager.

The already staggering cost of health care continues to escalate, and now represents 16% of the gross domestic product (GDP) in the United States, with estimates that unchecked, it could double again to 31% of GDP in the next 25 years [1]. Hospital costs are roughly a third of total health care costs, and intensive care alone consumes between 4% and 10% of total healthcare costs, or 0.56% to 1.5% of GDP [2–4]. One-third of Medicare patients spend part of their hospital stay in the ICU or coronary care unit, at an average unit cost per day of $2,616 (in 2004 US dollars) [5]. Discrepancies exist between the Medicare Provider Analysis and Review File (MedPAR) and the Hospital Cost Report Information System (HCRIS), two federal databases used to assess inpatient and critical care costs in the Medicare population [6]. In fact, critical care days may have decreased by 4.5% between 1995 and 2000 based on HCRIS data, while an increase of 7.2% was seen using MedPAR data, which includes "post/intermediate" billing codes [6]. Nonetheless, the Center for Medicare and Medicaid Services continues to forecast a substantial increase in the rate of growth in volume and intensity of medical services as the leading edge of the "baby boom" generation enters retirement [7]. Physician and nursing shortages [8] and increasing costs will constrain growth of intensive care services, while consumer demand (fueled in part by easy internet access to information) and an aging population with chronic disease will exacerbate existing capacity issues. New, unpredictable risks (e.g., novel bacterial and viral threats, terrorism) require preparedness and the ability to ramp up critical care capacity in a crisis. Meanwhile, attention continues to be focused on preventable medical errors. This confluence of events implies that attention must be paid to the health and well-being of the ICU in addition to addressing the needs of individual patients [9].

The conceptual frameworks [10] and business skills for successful ICU leadership must somehow be acquired, whether in business school or on-the-job. Important characteristics of leaders include self-awareness, self-regulation, motivation, empathy, and social skill [11]. The American College of Physician Executives is one organization that provides information on how to prepare for and succeed in medical management [12]. A formal Masters of Business Administration (MBA) program will typically include courses on accounting, data analysis, ethics, financial analysis, human resource management, information systems, marketing, production/operations management, organizational behavior, organizational planning and strategy, quality improvement, team building, and leadership. Given the difficulty in compressing a multiyear MBA curriculum into a book chapter, we will focus on typical ICU organization patterns, human resource issues, the roles of the ICU director, methods for monitoring clinical ICU care, and ancillary management issues.

ICU ORGANIZATION

In broad terms, there are three common models for ICU organization:

- **Open Unit:** Any physician with privileges to admit patients to the hospital may admit and care for patients in the ICU. Patient care decisions are made by the admitting physician, often with the input of consultants. Admission and discharge (triage) decisions fall to the unit director only in event of a bed or staffing shortage. Intensivists may be available for consultation at the request of the attending physician. The major perceived benefit of this model is continuity of care, and it remains prevalent in the United States, particularly in smaller hospitals.
- **Closed Unit:** All patients entering the ICU are transferred to the care of an intensivist (critical care specialist) for the duration of the ICU stay. Depending on local custom, the admitting physician may remain closely involved or collaborate from a distance. Benefits of this model include documented reductions in mortality, rates of complications, and ICU and hospital length of stay. This model is more common in Europe and Australia, but is gaining acceptance in the United States, based on research findings and response to external pressure from the Leapfrog Group [13] and payers.
- **Transitional (Semiclosed) Unit:** Patients are referred for ICU admission to an intensivist, who reviews all admissions for appropriateness (gate-keeping). Final decisions regarding admission, discharge and triage rest with the physician unit director or his or her designee. Either automatically, or by specific consultation, the intensivist may participate in some or all of the patient's care in conjunction with the patient's attending physician of record. The intensivist's role may be limited to triage functions and emergency response, but more often encompasses hemodynamic, respiratory, fluid,

nutritional, and safety management. This model is seen in the transition phase between open and closed structures, and remains common in surgical practices where the attending surgeon addresses the specific operative aspects of a patient's care (e.g., wound care, transplant immunosuppressive regimens) while delegating resuscitation, physiologic monitoring, organ system support and ICU safety issues to the intensivist.

Pronovost et al. [14] conducted a systematic review of articles examining physician staffing patterns and clinical outcomes published through 2001. The model of care in each of 17 studies was classified as low intensity (no intensivist or elective consultation) or high intensity (mandatory critical care consultation or closed ICU). The high-intensity model was associated with lower ICU mortality (pooled mortality risk estimate 0.61) and lower hospital mortality (pooled mortality risk estimate 0.71). Although the literature overwhelmingly favors intensivist staffing models, a recent retrospective analysis of the Project IMPACT database by Levy et al. [15] demonstrated *higher* odds for hospital mortality in patients managed by critical care physicians. These counterintuitive findings have been challenged as being caused by unmeasured confounders including case mix differences [16] and the role of trainees and part-time academic faculty [17]. The higher risk-adjusted mortality in *teaching* hospitals where more invasive interventions are performed [18] may also counteract beneficial effects of full-time intensivists.

Case-control studies, where outcomes have been examined before and after implementing a closed model, offer additional insight into the value of intensivists. Patients admitted to closed units tend to be sicker [19,20], as might be expected with tighter triage criteria, although average severity scores are not necessarily higher in closed units [21]. Nursing confidence in physician clinical judgment improves [18], as a closed system allows the nurse to contact one managing physician rather than having to call the pulmonologist for ventilator changes, the nephrologist for fluid and electrolyte issues, and the cardiologist for arrhythmias. (Although, as Marik et al. [17] have pointed out, detrimental "parceling out" of care may occur in an academic setting even when full-time intensivists are present). These efficiencies are generally reflected in shorter ICU and hospital LOS [19]. The effect of dedicated intensivist staffing on ICU LOS remains significant after case-mix is adjusted for risk factors such as patient age, admission severity of illness, pre-ICU length of stay and percentage of patients requiring mechanical ventilation [22].

Staffing patterns, in terms of in-house, overnight coverage, also vary widely [23]. The benefits of around-the-clock (versus business hours) in-house intensivist coverage is uncertain, despite outcome differences documented as a function of ICU admission time and day of week [24–28]. At the hospital level, there is no statistically significant mortality difference based on time of admission for most (77%) diagnoses [29], including acute myocardial infarction, congestive heart failure, pneumonia, stroke, gastrointestinal bleeding, and many surgical conditions. Mortality was higher, though, in patients with ruptured abdominal aortic aneurysms, acute epiglottitis, and pulmonary embolus, when these patients presented on the weekend. This suggests that for at least some conditions, adverse effects occur because of decreased weekend staffing, lack of patient familiarity with cross-coverage, and perhaps less supervision. Around-the-clock intensivist coverage may reduce severity-adjusted mortality [30] but there is debate if the on-site physicians need to be intensivists, especially given the current shortage of specialists [31]. Introduction of continuous on-site intensivists improves processes of care and staff satisfaction, and decreases ICU complications and hospital length of stay [32].

Remote intensive care, using a telemedicine approach, has been proposed as a partial solution to the shortage of intensivists. Using intensivists and physician extenders to provide supplemental monitoring and management of ICU patients between noon and 7 AM, Breslow et al. were able to demonstrate reductions in hospital mortality (RR 0.73), ICU length of stay (3.63 vs. 4.35 days) and lower variable costs per case [33]. Given the critical care shortage of intensivists, tele–ICU systems can potentially permit these specialists to monitor more patients, and those patients who might not otherwise have access to an intensivist. Despite the shortage of data, Leapfrog Group and the University Health System Consortium have encouraged the application of tele-ICU [34]. Results from the first federally funded multicenter evaluation of tele-ICU of approximately 4,000 patients from before and after activation of a tele-ICU did not demonstrate any differences in adjusted hospital and ICU mortality, length of stay or ICU complications with telemedicine intervention [35]. Of interest, improved survival rates were observed in the sicker population while mortality for less severely ill patients was increased. A major limitation of this multicenter trial include limited authority delegated to the tele-ICU by the majority of attending physicians; that is choosing to limit the remote specialists to monitoring rather than direct intervention authority. In addition, the inability to share the ICU electronic medical records with the central facility could have potentially delayed implementation of tele-ICU orders. The mixed outcome benefit of telemedicine for the ICU noted in recent trials [36] may indicate that the actual mechanisms of implementing telemedicine in ICU may play a significant role as to its effectiveness. Understanding and identifying local hospital wide operations including ICU staffing levels, evaluation of standardized care processes if any and availability of computerized order entry capability may help identify which ICUs benefit from tele-ICU.

A hospital's approach to ICU organization will depend on its patient population, existing professional talent, physical facilities, and economies of scale. Reimbursement for critical care and evaluation/management services typically cannot cover the cost of a dedicated intensivist in smaller units. Triage functions and general management of the unit (as opposed to management of individual patients) cannot be billed to patients, and thus does not generate professional revenue. However, there is ample evidence that hospital investment in physician intensivist services is recouped with better patient flow (reducing the need for additional ICU beds) and lower utilization of pharmacy, laboratory, and radiology services. Simply having an intensive care physician round daily on postoperative patients shortens LOS, reduces complications and lowers total hospital cost in patients undergoing esophageal resection [37] or abdominal aortic surgery [38]. Organizational restructuring of a cardiothoracic unit with an attending physician dedicated to ICU care resulted in reduced pharmacy, radiology, and laboratory utilization, and a per-patient decrease in hospital costs of $2,285 [39]. Pronovost et al. developed a financial model for 6-, 12-, and 18-bed intensive care units for hospitals transitioning over a 1-year period to the Leapfrog Group ICU physician staffing standard. Cost savings ranged from $510,000 to $3.3 million, depending on bed size [40]. Their best-case scenario results could generate up to $13 million in annual savings, while a worst-case scenario imposed net costs of $1.3 million.

PHYSICIAN HUMAN RESOURCE ISSUES

Hiring full-time critical care specialists is already a challenge with the growing shortage of intensivists. Critical care work force needs have not been adequately addressed by public

policy [41]. Medicare payments often do not cover the costs of providing critical care [42,43]. Angus et al. predicted in 2000 that supply and demand of intensivists would remain in equilibrium until 2007, but that demand would subsequently grow, producing serious shortfalls by 2020 [44]. The Society of Critical Care Medicine conducted a survey of 731 critical care physicians in 2004. These respondents planned to retire at an average age of 62 years, and to change focus or reduce patient load beginning in their fifties [45]. Nearly 40% of the respondents were already over the age of 45. Their average workweek was 66 hours, with a typical shift of 10 to 12 hours, providing clinical care an average of 48 weeks per year. It is unclear that the next generation of intensivists will continue to work at this level of intensity, or that critical care will be a viable career choice when remuneration is better for specialties with shorter working hours and less stress.

Current Leapfrog Group standards call for *in-house* intensivist staffing for a minimum of 8 hours, 7 days per week [13,46] or ≥2,920 hours per year to cover one ICU, with requirements for off-hours coverage met by an intensivist on beeper call, with an FCCS-certified physician or physician extender immediately available in-house. Hospitalists with FCCS certification can also potentially provide off-hours ICU coverage. In a retrospective study of care provided during after-hours coverage of a pediatric intensive care unit, Tenner et al. found improved survival with hospitalists compared with housestaff [47].

It is helpful to consider the concept of a clinical full-time equivalent (FTE) to represent the amount of work done by one individual working only on direct patient-care tasks in the intensive unit. In reality, some ICU clinicians will also allocate professional time to research, administration, or education; choose to work part time, or spend part of their clinical time on the trauma team, in the pulmonary clinic, or administering anesthesia. A full-time physician working only in the ICU might have grant funding for 0.25 FTE, and another 0.25 stipend for administrative and educational activity, leaving 0.5 FTE for ICU clinical activity.

How many hours will one FTE work in a year? The SCCM respondents' reports annual work hours from less than 1,000 to more than 4,000, but most commonly 2,000 to 2,500 hours [44]. Since attractive jobs currently offer at least 4 weeks vacation, about 10 paid holidays and at least 5 days of meeting time, we'll consider annual work to be 45 weeks with 10-hour days, yielding 2,250 hours, in accord with the range reported in the SCCM survey. If in-house coverage for the ICU is around-the-clock, 365 days per year, with 30 minutes overlap at the beginning and end of 12-hour shifts, then annual hours to be covered are 9,490. Thus, 4.2 FTEs would be needed to cover the clinical workload. This workload might be met by five physicians, assuming each worked full time and 0.8 FTE was sufficient to attend to administrative and quality assurance activities. If coverage is only during the daytime (3,650 hours per year) fewer FTEs would be required; although on-call hours must still be staffed.

Staffing calculations must consider intensivist-to-patient staffing ratios, which are not well-defined. In England and Wales, where intensivists staff 80% of ICU's, the average six-bed general ICU has three consultants committed to the unit, and another three consultants participating in the on-call rotation [48]. A retrospective study from the Mayo Clinic [49] did not find differences in the severity-adjusted mortality rate at daytime intensivist-to-bed ratios between 1:7.5 and 1:15 although ICU length of stay increased at the higher extreme. Larger hospitals with closed units may take advantage of cross-coverage between units, providing daytime care at intensivist to patient ratios of 1:8 to 1:12; and increasing the ratio during off-hours when there are fewer acute interventions or procedures to be accomplished.

MULTIDISCIPLINARY MODELS: PHYSICIAN EXTENDERS

The enormous work force requirements and economic burdens of providing round-the-clock critical care staffing has led physician leaders, hospital administrators, and insurance companies to re-examine models of health care delivery. Some medical centers now employ physician extenders on the critical care team as a response to physician shortage at both the attending and house-staff level. Physician extender is a broad term covering mid-level health care providers such as nurse practitioners (NPs) and physician assistants (PAs). Physician assistants must complete an accredited education program, usually 2 years in duration, but often requiring prior college and health care experience. PAs must pass a national examination to obtain a license, and always work under a physician's supervision. A nurse practitioner is a registered nurse who has completed advanced training and must be licensed in the state where practicing. Following state licensure, NPs may seek national certification from professional nursing boards and/or pursue specialty certification. NPs have more latitude to practice independently.

Driving forces that have accelerated employment of the physician extenders include cutbacks in federal funding for residency training, identifiable patient care needs, and ACGME standards placing strict limits to the number of hours that medical trainees can participate in providing care. Physician extenders can provide safe and cost-effective care as part of a collaborative medical management team in acute care settings and they are well received by patients, nurses, physicians, and administrators. A limited number of studies suggest that introduction of NP/intensivist team-based care is beneficial to patient outcomes, financial outcomes, length of stay, and patient satisfaction [50]. An attending physician/NP team can safely manage former ICU patients admitted to a subacute unit therefore allowing the intensivist/fellow team time to care for higher acuity ICU patients [51]. Decreased overall length of stay and ICU length of stay, lower rates of UTI and skin breakdown, and a shorter time to mobilization have been documented after introduction of an NP team to neuroscience ICUs [52]. NP participation in weaning protocols for mechanical ventilation has been associated with greater reductions in mechanical ventilation days, ICU length of stay, and hospital length of stay when compared to pre-NP participation [53]. NPs and physicians in training had equivalent efficacies in performing required tasks but residents spend more time in nonunit activities (lectures, rounds) and NPs spend more time monitoring patients, talking to families, and collaborating with other health team members [54].

A team-oriented culture characterized by timely communication is associated with a shorter length of ICU stay, greater ability to accommodate the needs of patient families, and a higher quality of technical care [55]. Including PAs on house-staff-directed ICU teams does not appear to affect rates of occupancy, mortality, or complications [56].

Intensive care services are among the most urgent and costly aspects of healthcare in the United States, and national surveys indicate the need to accommodate about 50,000 patients a day [43]. Professional societies are projecting an inability to meet this demand with intensivists, so the role of physician extenders will need to be further examined as a major component of the healthcare delivery model for critically ill patients.

ROLE OF THE ICU DIRECTOR

The Joint Commission on Accreditation of Health Care Organizations (JCAHO) requires that an individual be designated as the ICU Director, but actual job descriptions vary. At one

extreme, the medical director may simply approve critical care policies and serve as a resource for questions that cannot be solved by nursing administration. He or she may triage only in times of high census, and may have very little role in the delivery of critical care, other than to his or her own patients. At the other extreme, the medical director may lead the team of intensivists that assumes total responsibility for all patients occupying ICU beds. Nonclinical duties may consume more work effort than clinical responsibilities when committee membership, administrative tasks, budget preparation, educational activities, and the business of running the ICU physician practice are included. When the medical director is heavily involved in day-to-day operations, ICU occupancy rates and number of patients misallocated to ICU beds decline [57]. ICU admission decisions are only part of the triage function. One in six patients experience ICU discharge issues (unexpected medical deterioration, level of care issues, administrative problems [58]) that demand executive resolution.

Larger hospitals typically have multiple intensive care units, each with its own director. The directors or designees may participate in a hospital-wide Critical Care Committee that sets overall policies and procedures. In some units, the medical director may delegate administrative tasks, quality improvement, education, and research to associate medical directors. Typically, the ICU director(s) will have a close working relationship with the nursing unit manager in each unit. Multidisciplinary units will involve interaction with other professionals (pharmacists, dieticians, social workers, clergy, utilization management specialists) and the medical director may have an overall coordinating role. Essential character traits of the successful ICU director include willingness to collaborate, ability to delegate, trust in colleagues, and excellent communication skills.

Tasks performed by the ICU Director can best be divided into strategic versus tactical (Table 208.1). Strategic tasks involve the "big picture": recognition of patterns and trends, setting priorities, considering alternatives, and implementing change. The ICU Director is often the champion for process improvement projects. Areas deserving of strategic consideration include cost containment, the overall culture of the ICU, quality improvement efforts, education of physicians, nurses and other health professionals, and coping with change driven by ICU, hospital and external factors [59]. Developing a strategic vision and communicating it well are essential roles. Yet, it is equally important to lead by example, particularly when it comes time to drive change, such as implementing electronic medical records or computerized physician order entry.

Tactical chores consist of the day-to-day, "hands-on" running of the unit. Leaving aside patient care, which in itself can fill the day, there are issues of personnel coordination, patient triage, bed allocation, and conflict resolution [60]. The ICU director is often granted by hospital policy the authority to intervene in any patient's care, and may be charged with evaluating issues and complaints that originate from family members, nursing staff, other physicians, or hospital administration. Tools to assist with the tactical aspects of patient care include checklists [61] and computerized systems. The danger is that tactical chores multiply to occupy all available time, leaving little time for strategic direction. Implementation of computerized order sets, therapist-directed protocols, and other "bundles" of care help to minimize the individual, routine tactical decisions, and leave more time for strategic thinking.

The difference between strategy and tactics reflects the difference between leading and managing. Applied to academic teaching rounds as an example, the residents or physician assistants should be patient managers responding to the information flow of physical exam findings, laboratory tests, and radiology reports. They collect and analyze this data, and develop a daily or even hourly plan. In contrast, the attending physician or fellow should not get lost in the details, but rather should be planning at a higher level exactly what broad changes and interventions will be required to get the patient recovered and discharged from the unit. It is difficult to concentrate on both tactics and strategy at the same time, which argues for dividing the effort with a team approach. The strategic leader should not be isolated from patient contact, however, for it is the experienced interpretation of clues and subtleties that define the expert [62].

The job responsibilities of the ICU Director (and by delegation, the triage physician of the day) create an inherent conflict of interest. A treating physician's fiduciary responsibility is to advocate for an individual patient's best interest. As the ICU manager, however, there is a responsibility to do the most good for the greatest number of patients. The essence of triage is to maximize benefits for the group, even at the expense of an individual. In times of bed shortages, the ethical principle of beneficence ("do good") conflicts with the ethical principle of social justice. For example, a 92-year-old patient has a cardiac arrest at home, and arrives intubated and ventilated in the emergency room with fixed pupils but slight respiratory effort. Although the outcome is uncertain, it certainly does not look promising. Should the last remaining ICU bed go to this patient who is unlikely to survive, if it means refusing a complex hospital transfer, canceling an operating room procedure, or denying ICU admission to a septic patient on a regular nursing floor? These ethical issues are discussed elsewhere in this text, but it is essential for the ICU director to recognize these conflicts and preemptively construct ICU and hospital policy to address how such conflicts are to be handled.

TABLE 208.1

STRATEGIC VERSUS TACTICAL DUTIES OF THE ICU DIRECTOR

Strategic	Tactical
Creating ICU vision and mission statement	Conflict resolution, communicating vision
Evaluating and improving quality of care	Implementing care "bundles" and protocols
Right-sizing physician workload	Hiring new staff; creating call schedule
Fostering interdisciplinary relationships	Interdisciplinary rounds. Joint conferences
Planning for the future	Budgeting; space and equipment needs
Delivering value	Specific cost-containment initiatives
Economic self-sufficiency of practice	Monthly review of financial statements
Professional development	Physician and nursing education
Efficient resource management	Bed triage: written policies
Exploiting advanced technology	Implementing electronic medical records

BUDGET AND PROFESSIONAL REIMBURSEMENT ISSUES

The ICU director may be responsible for managing the budget of the entire critical care unit, including the nursing and respiratory therapy components, but if so, will usually have administrative assistance. More typically, the division chief in an academic ICU or the director of a practice group will be

particularly concerned with revenue from physician professional activity. Particular attention must be paid to actual revenue received since the net collected will always be less than gross professional billing, a problem that is increasingly worse with the current system for physician payment based on the Medicare sustainable growth rate [63].

In the United States, critical care revenue is generated by billing critical care codes (CPT code 99291 and 99292) when the patient qualifies for time-based bedside critical care, or otherwise for Evaluation and Management Codes (typically CPT code 99232–33 for subsequent hospital care, and 99251–53 inpatient consultation) [64,65]. Various procedures have specific codes, and each code is associated with relative value units (RVU) that form the basis for eventual payment. Further information on CPT coding is available on the AMA Web site [66] and through the American College of Chest Physicians [67], among other sources. The relationship between total RVU and CPT codes change over time. For example, insertion of a pulmonary artery catheter generated 3.79 total facility RVU in 2006, but only 3.08 RVU in 2009. On the other hand, CPT 99291 (Critical Care, first hour) was worth 5.99 RVU in 2009, up from 5.48 in 2006. Despite the 9% increase in RVU for this code, however, reimbursement only increased a little over 1%. Critical care physicians must constantly monitor the coding and reimbursement landscape. As of January 1, 2010, the Center for Medicare and Medicaid services (CMS) eliminated all inpatient and outpatient consultation codes. It is anticipated that other insurance carriers may adopt these changes going forward, but as of this writing, consultation codes are still valid for most non-CMS claims. In the interim, providers (or their billing offices) have to pay careful attention to how claims are submitted, depending on a patient's insurance status. Demonstration projects are already underway to move away from RVU piece-work to a global, or bundled, payment system [68].

The connection between RVU generation and effort in the ICU setting in any case is tenuous at best, in part due to the difficulty in documenting and billing the multitude of small tasks accomplished over the course of the day. The bulk of billable services may occur during the normal business day. Thirty-one to seventy-four minutes of bedside attention to one patient will justify a single CPT 99291 code. Additional services rendered to that patient throughout a 24-hour period would have to exceed 74 total minutes to additionally bill CPT 99292. As a result, off-hours interventions may generate less income than what it costs to staff those hours, although revenue will depend on the number of patients seen, their severity of illness, and the reimbursement rate for a particular locale. In many institutions, revenue received may be 50% or less of what was actually billed, owing to indigent patients and contractual agreements with insurers. Thus, under systems of reimbursement used in the United States, it may not be possible for a critical care physician group to be self-funding on patient care revenue alone especially when providing extended hours of in-house coverage.

The ICU director plays an increasingly important role in managing the business aspects of the critical care practice. It is helpful to have a tracking system to ensure that each physician is submitting his or her patient care charges in a timely manner, and that the billing service is properly submitting and capturing these charges. On a monthly basis, patient care volume, charges submitted and relative value units (RVU) should be reviewed and compared with budgeted amounts. Individual physician performance by billing code should be tracked, not only for productivity, but also to ensure that codes are being used appropriately and in line with the practice's usual profile. It would be unusual for all patients to qualify for critical care codes; some percentage of patients may only qualify for E&M billing, with or without additional procedures. Periodic internal audits help confirm physician compliance with Medicare and insurer billing rules; it is easier and less costly to identify and rectify any issues internally. The alternative may be an external audit, where any errors detected in a small sample of charts will be applied proportionately over a multiyear period to demand a large retrospective repayment for billing errors. A provision in the 2009 American Recovery and Reinvestment Act of 2009 mandates annual fraud and abuse training for health care providers.

The Centers for Medicare and Medicaid Services (CMS) have recently implemented a Recovery Audit Contractor (RAC) program to review billing and identify over- and underpayment [69]. Four regional auditing firms will be paid on a contingency basis to review medical record documentation, especially the diagnostic specificity of admitting and discharge diagnoses, listings of comorbidities, and evidence of medical necessity as patients transition from care environments (operating room, recovery room, emergency department, inpatient vs. observation status). Service level is likely to drive reimbursement more than patient location. The coding of diagnosis-related groups (DRGs) will come under particular scrutiny. DRGs likely to trigger review include many common ICU conditions including sepsis (versus infection alone); acute respiratory failure (versus acute systolic or diastolic heart failure), pneumonia, chest pain, and stroke (versus transient ischemic attack).

ICU directors are frequently asked to represent the ICU on multiple hospital committees, particularly pharmacy and therapeutics, informatics oversight, quality improvement, peer-review, and technology assessment. Depending on the hospital's structure, the ICU director may report to the chair of Medicine, Surgery, or Anesthesia (or all three!) and frequently interact with Emergency Medicine, Obstetrics, Radiology, Laboratory Medicine, Clinical Engineering, Information Systems, Risk Management, and Nursing. A "virtual" critical care department can monitor and manage all critical care activities, while retaining a traditional academic reporting structure [70]. Responsibilities of the ICU director include developing a team performance framework for the unit [71], and addressing the physical, emotional and professional elements that create an attractive and rewarding ICU work environment [9]. These communication and collaboration activities take time, and, not surprisingly, administrative and other non-patient care activities may consume 50% or more of the ICU Director's work hours. Since this time is not revenue generating, these activities must be supported by other means such as a hospital stipend.

MONITORING CLINICAL CARE

Good structure (attributes of the setting in which care occurs) facilitates good process (what is actually done), which promotes good outcome (or results) [72]. Although the JCAHO historically focused on structural elements such as medical staff organization, available equipment, and human resources, emphasis has now shifted to analysis of process and outcome. Performance variables (appropriateness and effectiveness of care) may offer advantages over outcome variables for ICU evaluation, but are less well developed [73]. Most benchmarking currently takes place by outcome assessment, commonly using mortality and resource utilization as endpoints. Because patients present with different levels of disease and physiologic reserve, raw outcome measures such as mortality must be adjusted for severity of illness [74]. For the ICU, tools include the Acute Physiology and Chronic Health Evaluation (APACHE) system [75–77], and the Mortality Probability Models (MPM) [78,79]; the Simplified Acute Physiology Score (SAPS) [80,81], and the Intensive Care National Audit and Research Centre (ICNARC) model [82]. These systems are based on large

databases, report acceptable discrimination and calibration, and have been extensively examined in the peer-reviewed literature. However, only a minority of hospitals (about 10% of acute care hospitals in the United States) consistently collect this type of data. Although APACHE and MPM are generally used in North America, SAPS in Europe, and ICNARC in Great Britain, models can be employed in any location as long as the model is recalibrated for the local environment [83].

ICU severity models facilitate comparisons between intensive care units, and are most useful for retrospective analysis of performance, with limited but improving utility for real-time management. (APACHE, for example, offers a "bed-board" that displays both current severity of illness and daily predictions for mortality, discharge, and next-day resource utilization but unless this is interfaced to the electronic medical record, updates depend on coordinators entering updated information.) Project IMPACT (which uses the MPM prediction model) and the APACHE system each carefully define data elements and outcomes to be collected, and thus facilitate comparison of local outcomes with national data. APACHE provides the ability to run local comparison reports on an ad hoc basis; comparison reports from Project IMPACT are centrally generated on a quarterly schedule. APACHE, SAPS, and MPM have all recently transitioned from models based on 1990's data to updated versions that reflect changes and improvement in medical practice over the past 15 years [76,78,80].

An APACHE IV score comprises the Acute Physiology Score ("APS," see later), age, and chronic health items. The APS is generated by summing point values based on physiologic derangement in 17 variables and then adding points for age and chronic health status [76]. The APS is interpreted in light of the main patient diagnosis, patient location, and duration of hospital stay prior to admission to the ICU. Mechanical ventilation during the first ICU day and emergency surgical status also influence an individual's predicted mortality. Although the error bars around the mortality estimate are modestly large for any individual patient, the APACHE system has been shown to be quite reliable at assessing outcome for groups of patients [76]. APACHE IV is also useful for assessing ICU length of stay in groups of patients even though utility is limited for individuals [84].

Project IMPACT, developed by the Society of Critical Care Medicine, began collecting data in 1996 and providing benchmarking with the MPM-II model, SAPS-II, and APACHE II. Beginning in 2007, Project IMPACT transitioned to the updated MPM-III model [85]. Project IMPACT data collectors must pass a certification examination to access the data entry module. The MPM-III model has been prospectively validated using recent Project IMPACT data from 55,459 patients at 103 participating ICU's in North America [86]. As of this writing, plans are underway to consolidate the APACHE system and Project IMPACT into a single critical care information system that will take advantage of the ease and immediacy of the MPM score (generated on admission) with the more detailed, disease-specific predictions of the APACHE system at 24 hours and beyond.

Specialized scoring systems are more appropriate for pediatric [87], trauma [88,89], or cardiac surgical units [90]. Pediatric scoring (e.g., PRISM) differs from adult scoring due to expected differences in normal physiologic ranges. Cardiac surgical systems downplay acute physiology, which is deliberately controlled by the operating room team, and emphasize variables such as left ventricular function, IABP use, and cardiopulmonary bypass (CPB) time that might not be available or clinically relevant in other patient groups. Performance of the general severity models deteriorates when case-mix in an ICU becomes skewed [91]. APACHE-IV accommodates case-mix differences by including disease-specific coefficients. MPM-III provides sub-group models for use when an individual ICU's case-mix is skewed from average [92], although the general model is essentially as good as specialized models for identifying outliers.

The primary clinical limitation of all outcome-adjustment models is that they apply to analysis of outcome in groups of patients, but not when making individual therapeutic decisions. At best, the prognostic estimates for an individual patient may be used in a probabilistic manner to predict bed or other resource utilization, but could be inaccurate if applied as a prediction for application or denial of individual medical therapy, because of the uncertainty of individual estimates. A patient's risk will change over time, making it problematic, for example, to use the admission severity score to determine eligibility for later therapy [42]. In fact, ICU physicians discriminate between survivors and non-survivors more accurately than scoring systems, at least in the initial 24 hours of care [93].

Groups of patients can be compared by generating predicted mortality rates with APACHE, ICNARC, MPM, or SAPS as a tool, and comparing the prediction with actual results. The ratio of observed mortality to predicted mortality is called standardized mortality ratio (SMR), and an ICU with a SMR close to 1.0 would be exhibiting expected performance based on their case-mix of patients. SMRs significantly greater than 1 indicate a higher than expected mortality whereas SMRs less than 1 suggest outcomes better than expected. The sample size and distribution of patient acuities will determine exactly how far from 1.0 (in either direction) the SMR becomes significant.

Events and therapy prior to ICU admission that alter physiology at admission creates a "lead time" bias which has a measurable effect on outcome [75,94]. Because the SMR will be affected by differing use of postacute facilities and the percentage of patients with DNR orders, it may not always be valid in interhospital comparisons, unless applied to similar types of hospitals with similar policies [95].

Both clinical performance and cost-effectiveness should be considered when defining high-quality ICU care [96]. Rapoport and Teres initially described a method, since updated [97] that graphically displays both severity-adjusted clinical outcome and cost-effectiveness, using weighted hospital days as a proxy for cost. With this method, normalized severity-adjusted mortality is displayed on the *x* axis, and normalized weighted hospital days on the *y* axis (Fig. 208.1). Standard deviations of the normalized scale are displayed relative to the group mean at the origin (0,0). Units performing significantly better than predicted for both dimensions of care will chart in the right upper quadrant of the graph.

CRITICAL CARE OUTREACH SERVICE AND EARLY WARNING SYSTEMS

Illness is commonly heralded by a constellation of quantifiable changes in physiologic and biochemical measurements. Abnormal values of selected physiologic measurements are useful as an objective indication of a patient's risk level (as with severity scores) but may also be used "real-time" to predict subsequent clinical deterioration on hospital wards. In theory, if hospital staff were to identify and provide intervention to these patients at an earlier stage, outcomes could improve, in terms of reduced intensive care admissions and length of stay. Critical Care outreach services include the employment of a Rapid Response Team (RRT) and/or an Early Warning System (EWS) to identify and provide intervention to potentially deteriorating hospitalized patients. The fundamental concept behind the evolution of Critical Care Outreach Programs is that significant vital sign abnormalities occur in many patients in the hours prior to acute cardiorespiratory events [98,99]

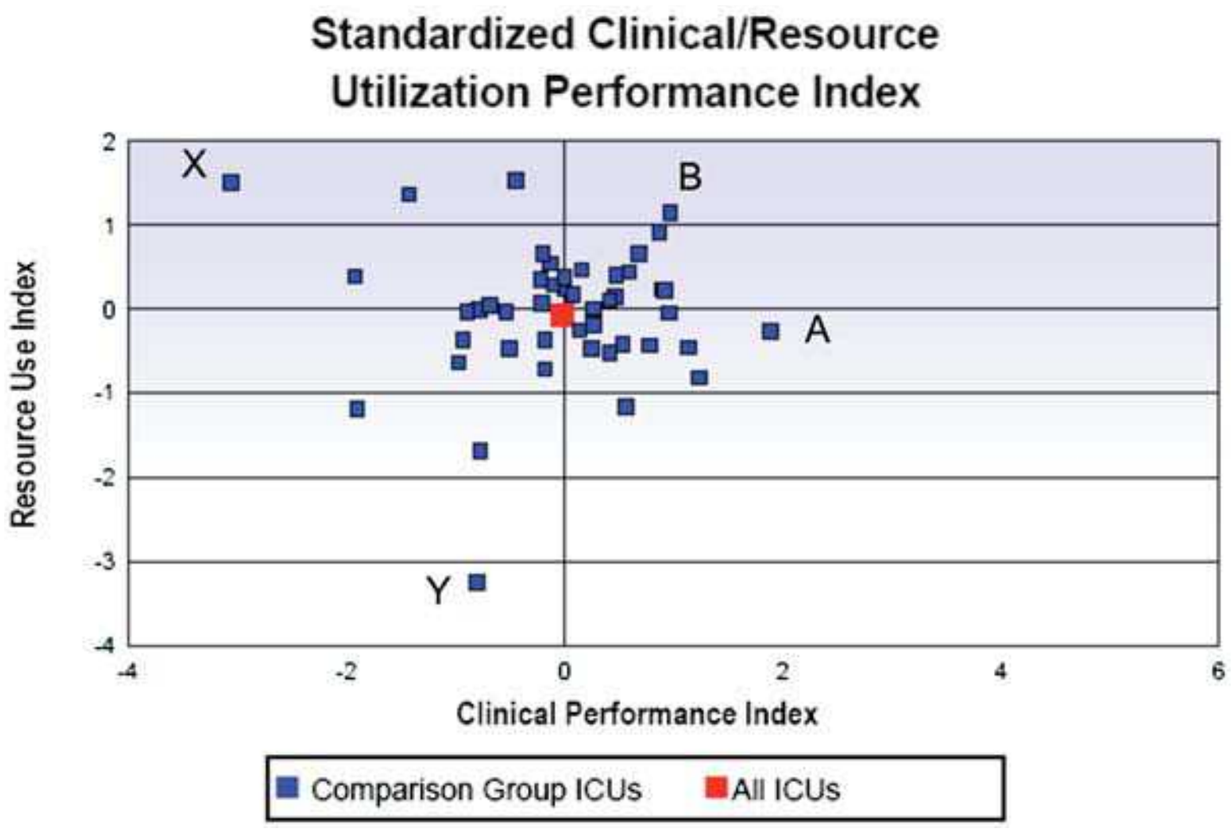

FIGURE 208.1. Standardized Clinical/Resource Utilization Performance Index. Hospital A has superior risk-adjusted mortality, while hospital B has superior risk-adjusted length-of-stay. Both hospitals are in the desirable right upper quadrant. Hospital X has a short length of stay, but coupled with risk-adjusted mortality that is worse than predicted. Hospital Y has length-of-stay issues while remaining within the expected severity-adjusted mortality range.

Analysis postimplementation of a RRT model of care (also called Medical Emergency Team or MET) on hospital wards demonstrates 17% to 50% fewer cardiorespiratory arrests [97,98,100]. The composition of a RRT/MET varies by hospital but frequently includes an ICU nurse and/or physician, a hospitalist, and a respiratory therapist. The Institute for Healthcare Improvement has recommended that hospitals establish RRTs as one of the six strategies of the 100,000 Lives Campaign [101]. Though the purpose of the RRT is to reduce preventable deaths [102], evidence supporting their effectiveness remains controversial [103–105]. Clinical trial results have suffered from methodologic limitations, varying staffing models, and limited number of randomized control trials. A recent trial could not document reductions in hospital-wide code rates or mortality but did demonstrate fewer cardiorespiratory arrests outside the ICU [106]. It is possible that the RRT involvement may propel end-of-life discussions in patients on the wards that might otherwise not have taken place. Further comprehensive investigations of the expanding RRT model will require better data on hospital characteristics, assessment of patient–family satisfaction, assessment of end-of-life issues, and nursing and physician satisfaction on the wards.

EWS incorporate technology to provide earlier identification of patients at risk of clinical deterioration on general hospital wards [107,108]. Although clinicians generally excel at detecting acute change, incremental changes in vital signs may not be clinically apparent, but become obvious using tracking software. A "track and trigger" EWS is designed to secure the timely presence of skilled clinical assistance by the bedside of patients exhibiting physiologic signs compatible with impending critical illness [109]. Although RRT responses might be triggered by a single dramatic physiologic vital sign change, EWS responds to simultaneous multiple parameters using patterns of subtle alterations in vital signs to identify patients at risk [110]. An automated EWS score is calculated from a handful of traditional physiologic parameters (mental status, heart rate, blood pressure, respiratory rate, temperature, urine output) recorded with traditional bedside or electronic charting [111]. Several readings over time may be more informative than isolated recordings. Newer bedside physiologic monitors (for example, Philips MP Series with ProtocolWatch) [112] can automate this process without requiring a full electronic medical record. Although recent data indicates that EWS integrating information from multiple physiologic variables is better at detecting physiologic instability [113], the diversity and methodologic limitations of most studies to date limit the ability to interpret the effectiveness of EWS application in hospitals.

Failure to identify clinical emergencies may be becoming more frequent as sick patients cannot always be accommodated in critical care units. High-quality multicenter research will be needed to determine the most appropriate triggers for activation of the EWS and/or RRTs and the effect of these interventions on patient outcomes. Because EWS and RRT deployment will affect ICU resource utilization, ICU leaders need to be involved in planning, implementing, and maintaining these systems.

OPERATIONAL ISSUES

Nursing staffing levels are now subject to public scrutiny, and literature supports a link between staffing levels and patient outcome. Excessive nursing workload has been shown to correlate with increased mortality [114], longer hospital length of stay and increased complications [60], and the spread of resistant bacterial organisms in the ICU [115]. Adverse events have been reported to occur in about 20% of critically ill patients, with roughly half reportedly being preventable [116]. The most common cause of an adverse event is failure to carry out intended treatment correctly, often because of miscommunication or poor coordination of care [117]. Some hospitals have explored crew resource management training, adapted from the aviation industry, to improve team collaboration and coordination, and ultimately improve patient safety. The medical director, in conjunction with the nurse manager and other professionals, will play a major role in defining and maintaining the organizational culture of the ICU. Disruptive physician behavior adversely affects nursing retention [118] and occasionally will require the intervention of the medical director, perhaps with the assistance of the hospital's Physician Health or Medical Staff Health committee. Effective teamwork is essential, and team leadership is vital in promoting team interaction and coordination [70].

Interdisciplinary communication is fostered by a number of formal and informal efforts. At a basic level, the format for daily ICU rounds should encourage all members of the team to contribute information, ask questions, and make suggestions for the direction of care. Formal multidisciplinary rounds, often held weekly, are useful when discussing the needs of long-term patients in the ICU, and offer an opportunity to step back from acute physiologic concerns to collect additional insight from allied health professional, social service and clergy. Conferences, journal club, lectures, and research projects offer opportunities for beneficial interdisciplinary interaction. Some hospitals have

established a Critical Care Practice Committee (CCPC), composed of physician and nursing representatives from each intensive care unit, the emergency department, and the postanesthesia recovery unit. Members of this committee may also include representatives from Pharmacy, Central Supply, Clinical Engineering, Respiratory Therapy, and Purchasing. A hospital-wide CCPC facilitates standardization of policies and procedures [69,119], implementation of care bundles, decisions on supplies to be stocked, maintenance of "Code" carts, and quality improvement initiatives relevant to the membership [120].

Patient families deserve special consideration; especially since the family is likely to notice and appreciate the operational efficiencies and communication style that reflects the ICUs culture. A multicenter evaluation of a scoring system for family satisfaction [121] identifies the key components for family satisfaction as assurance (the need to feel hope for a desired outcome), proximity (the need for personal contact and to be physically and emotionally near the patient), information (which should be consistent, realistic and timely), personal comfort, and support (resources, support systems and ventilation). Written materials (booklets, information sheets) can help meet family informational needs, especially with older, better educated relatives [122].

SUMMARY

Economic considerations continue to drive the agenda in hospitals and intensive care units, and with the wave of "baby boomers" reaching retirement, increasing incidence of obesity, diabetes and vascular disease in the population, and sporadic emergence of new threats, such as pandemic threats like the H1N1 strain of the Influenza A virus, we can expect further change. With a sicker, more chronically ill population, hospitals have become places for the hyper-acutely ill, with much of recovery and recuperation outsourced to other facilities. Thus, intensive care will continue to consume an ever-greater proportion of total hospital costs, even as this growth becomes constrained by economics, bed shortages, and most importantly, insufficient numbers of nurses and physicians specializing in critical care. In many hospitals, what was once the province of the ICU has migrated to step-down and specialty units, leaving the ICU populated by the sickest of the sick. The advent of hospitalists and rapid response teams are but two manifestations of this continuing evolution in how care is delivered. These changes have forced a re-evaluation of ICU organizational practices (increasing the value of "closed" units), human resource needs, a more management oriented role for the ICU director, and critical care management approaches that involve professionals from more than one ICU. Benchmarking critical care outcome becomes essential in managing the increasingly complex world of the ICU, and we are on the threshold of having computerized real-time systems to automate some of the tactical decisions that occupy too much professional time. Telemedicine, increased automation, use of physician extenders and protocol supported care are all potential solutions to the impending crisis in critical care delivery. Continued change emphasizes the need for clinically and managerially competent physicians to organize and manage the increasingly complex world of critical care.

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CHAPTER 209 ■ CRITICAL CARE INFORMATION SYSTEMS: STRUCTURE, FUNCTION, AND FUTURE

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INTRODUCTION

In over five decades since the first implementation of the electronic health record (EHR) in the United States, there have been both the rise, definition, and establishment of critical care medicine as a specialty and important force in health care both in research and practice.

Although technology has played an essential role in the very creation of the specialty (e.g., ventilators, cardiovascular monitoring), the implementation of the EHR in U.S. hospitals, and, as per available data sources, in intensive care units (ICUs), remains at a meager 1.5% [1].

With the American Recovery and Reinvestment Act (ARRA), the HITECH section promises to stimulate "meaningful use" of information technology (IT) in U.S. hospitals. This is the greatest single transformation ever undertaken of the information infrastructure of U.S. health care.

This chapter reviews a number of key components of IT in the modern U.S. ICU. The reader is introduced to some of the most important innovative technologies that have been brought to bear on the safe, effective, and efficient delivery of critical care medicine.

General information on the electronic medical record, departmental information systems, and coding and billing information systems has been extensively documented elsewhere and we assume a working knowledge of these basic components of the modern healthcare information infrastructure. Instead, we concern ourselves with the ICU-specific IT of greatest interest to the practicing critical care physician.

In this chapter, we address (i) telemedicine in the ICU, (ii) clinical decision support systems, and (iii) outcomes' prediction information systems.

TELEMEDICINE AND THE INTENSIVE CARE UNIT

According to the Military Health System Web site, telemedicine may be defined as "an umbrella term that encompasses various technologies as part of a coherent health service information

resource management program [2]. Telemedicine is the capture, display, storage and retrieval of medical images and data towards the creation of a computerized patient record and managed care. Advantages include: move information, not patients or providers; enter data ONCE in a health care network; network quality specialty health care to isolated locations; and build from hands-on experience."

Critical care information systems (CCIS) have largely overcome the technical barriers to their implementation. While there are enormous amounts of data available and opportunities to enhance the delivery of critical care, it remains challenging to marshal those resources in ways that meet the needs of both hands-on caregivers and overall delivery system efficiency and quality.

There are two large categories in which clinical information systems technology can be deployed and each is enhanced by the use of the other approaches. These are (i) single-patient–focused tools and (ii) multiple-patient–focused tools.

Single-Patient–Focused Tools

The most mature implementation of critical care clinical information systems consists of tools which meet the needs of the hands-on caregivers. Historically, massive amounts of data documenting an ICU patient's clinical status and treatment have been recorded on large double-sided paper flow sheets, which are plagued with problems of legibility, inaccurate calculations, and use restricted to a single person at a time. By replacing this document with computer screens, each customized to a specific purpose, these problems have been essentially solved.

Going beyond simple replacement of paper documents provides an opportunity to present information such that patterns are more easily recognized. For example, correlation of measures of physiologic status, clinical status (such as urinary output and body weight), and administration of medications can facilitate clinical analysis by juxtaposing interdependent variables. Less obviously, trends over longer periods of time can be easily displayed while these could only be laboriously drawn by hand.

Optimal use of clinical information systems should also guide the hands-on caregivers to provide care using evidence-based protocols. Simply creating a place to document the position of head of the bed underscores that this is important issue to be managed in prevention of ventilator-associated pneumonia (VAP). Explanatory information can also be provided on a just-in-time basis to encourage protocol compliance. Computer provider order entry prompts and order sets can also facilitate standardization of care.

Simply collecting and displaying information electronically, while an advance over a paper record, vastly underutilizes the capability of the computer system. The data are being gathered in a computable form and consequently are subject to continuous analysis, enabling detection of patterns that could signify clinical decompensation. Vastly larger datasets than can be retained and analyzed in the human brain can be evaluated and, furthermore, it can be done continuously on all monitored patients, simultaneously. Such an early warning system could trigger evaluation that might otherwise be delayed.

Finally, computable information that describes in detail both the patient's status and treatment can be used to analyze compliance with protocols for optimal care, resource utilization, and outcomes. Monitoring on a near real-time basis provides timely feedback and is an opportunity to intervene to improve ongoing care.

Once all of these capabilities are available and used by the hands-on caregiving team, their individual capabilities can be optimized. Nonetheless, the realities of the critical care environment are such that patients may be critically ill and yet not be in a setting where their care needs can be expeditiously met. For example, a patient might be in a distant hospital where intensivist coverage is not available. Or, even in a sophisticated medical center, patients may decompensate outside the ICU and, indeed, even in the ICU after hours, an intensivist might not be physically available to respond.

Two technological approaches to dealing with this problem have developed, each dependent on a suitably trained intensivist sitting at a remotely located computer that is equipped with a microphone and speaker and a high-bandwidth Internet connection. Each approach also has one or more high-resolution cameras which can be controlled by a remote physician and means to communicate with caregivers and patients and family who are in the patient's room. Medical devices such as stethoscopes can sometimes be connected as well.

Connectivity to additional clinical information systems varies according to institutional capabilities. For example, some systems have as many as eight monitors arrayed such that the remote physician can see the real-time electrocardiogram tracing, access the institution's image archiving and communication systems, and review all elements of a comprehensive clinical information system, simultaneous with viewing and talking with the patient. Without question, availability of this full suite of technological capabilities allows a comprehensive evaluation of the patient that far surpasses the limited verbal interaction between the bedside caregiver and a physician connecting by telephone. It is now well documented that such interactions can provide for more timely and therapeutically appropriate interventions [3]. Nonetheless, such evaluations are still limited in that hands-on physician diagnostic and therapeutic maneuvers are not available when the physician is remote. It has been documented that remote proctoring of a procedure being performed by a house officer who is in the hospital is a practical alternative when immediate interventions are required. Furthermore, even in the case where the physician or patient will need to travel to the point of care, useful temporizing measures may be deployed.

A form of technology that is particularly well suited for the interaction with an individual patient is a mobile robot, offering what is referred to as "robotic telepresence." One form of this device can actually be driven remotely by the physician from its storage location to the patient's location in the appropriately equipped facility. Using wireless connectivity, the robot establishes a similar connection to that which exists in rooms that have been specifically hardwired for these capabilities. Because of the costs of connectivity, institutions frequently limit fixed installations to ICUs. Nonetheless, it is clear that patients in other patient care locations can decompensate and care may be needed elsewhere. Such robots provide a lower cost means to provide similar capabilities and could be used to augment the expertise of rapid response teams.

Interactions may be initiated by the caregiving staff from any care location. In such circumstances acceptance has been generally very favorable. Nurses feel that there are trained physicians who are awake and available in the middle of the night and can be provided with all of the information needed to provide care. As a consequence, nurses may be more confident that the patients are receiving quality care. A limitation is that the remote physician may have less of an appreciation for the patient's clinical course than a physician who has seen the patient daily. However, in some ICUs, the physician on call at night at home and using the robot may be the same person who rounded on the patient that day. Interaction between remote and primary treating physicians remains an essential element of care.

Multiple-Patient–Focused Tools

In institutions where multiple ICUs have been equipped with cameras in each room and connectivity to clinical information systems and other clinical data sources has been established, a

team is established at a central monitoring location which may be distant from the ICUs and hospital(s), frequently off campus in less-expensive commercial office space. Analysis of signals from bedside monitors and other devices as well as the results of laboratory tests alert off-site providers to perform patient assessments. Alternatively, bedside providers can request evaluation and off-site management. Interventions, including the ordering of diagnostic tests, medications or consultations, or the manipulation of life support devices can be done by off-site providers or by on-site providers. Thus, a single patient interaction may be initiated by the remote physician as well as by hands-on caregivers. Like any team endeavor, effectiveness is determined in part by communication timeliness and dynamics of trust and responsibility among the bedside and off-site team members.

The primary responsibilities of the remote monitoring team are identification of unfavorable trends and to intervene to enhance best practice adherence, perform care plan reviews for patients admitted after day time hours and provide ICU pharmacist [4] review of after hours provider medications orders which provides an additional safety net for patients in the ICU [3,4]. Bedside caregivers have the potential to be overwhelmed by the need to care for multiple patients, and the requirement to deal with the mechanics of providing care may interfere with always maintaining perspective on the patient's course.

Information systems that power the central monitoring station have been equipped with series of rules that evaluate clinical information as it is being gathered at the bedside and returned from the laboratory. By correlating this data, alerts can be fired to draw the attention of the remote monitoring team. The team then has the clinical information available to judge whether this is a new or serious development which then prompts interactions with the bedside caregiving team. Such tools may also be available to the bedside caregiving team; however, their many clinical duties can often result in a delayed response. Furthermore, many bedside clinical information systems are much less sophisticated in this area than are the systems designed for use in monitoring a population of patients.

An important capability is the opportunity to perform virtual rounds on the sickest patients. The acuity status is used to identify which patients might most benefit from closer observation. In this way, the remote physician can perform virtual rounds at intervals to judge the effect of medications which may have been administered to determine if physiologic responses are improving or deteriorating. This surveillance can be an important complement to bedside care.

An essential element for the success of remote monitoring of critically ill patients is the effective collaboration between the hands-on caregivers in the central monitoring team. The bedside critical care multidisciplinary team that is responsible for the patient and sees the patient and family on an ongoing basis is best positioned to establish the daily plan of care for each patient. The role of the off-site team members is to keep the patient on the intended trajectory and to communicate with the bedside providers when the patent's course has deviated from that path. In ICUs where full-time 24-hour day coverage is not available, which is the vast majority of ICUs, physician interaction that may be necessary to ensure that the goals of care are achieved may be sporadic and untimely. The remote team serves as a surrogate for the bedside team at times when they are not able to attend to the patient. In recent years, evidence has accumulated that ongoing availability of intensivist is associated with improved outcomes. If there are an insufficient number of trained intensivists to cover the ICUs that exist, such remote monitoring is being used to increase the availability of trained staff.

It has also been established that implementing certain protocols for care of critically ill patients is associated with better outcomes in the management of sepsis and the avoidance of VAP. Nonetheless, it has proven challenging not only to achieve initial compliance with such protocols, but even more difficult to maintain compliance at a high level. An additional role played by a central monitoring team is to identify when patients who are eligible for a protocol are not receiving such care.

To the extent that the remote monitoring team functions completely independently from the on-site caregivers, there is opportunity for miscommunication and compromise of trust. Indeed, bedside caregivers have been reported to feel threatened by the sense of someone looking over their shoulders all the time and the primary treating physicians could resent intrusions that alter the plan of care set out by them [5]. A substantial investment in relationship building and acceptance by all members of the on-site and remote teams of the importance of minimizing medical errors is thought to be associated with larger improvements in outcomes.

In the fall of 2009, a new technological sea change is that the Blackberry and Apple iPhone are beginning to not only take over the previous place of the medical pager, but, due to their ubiquitous access to high-speed Internet, provide the means to deliver high-resolution bedside monitoring device (BMDI) data, as well as complete access to the electronic medical record from any location at any time. Although telemedicine has enabled new healthcare structures, as mentioned earlier, these new technologies delivered to the individual practitioner are likely to transform medicine just as has happened in the business world [6].

ANALYSIS OF DELIVERY SYSTEM PERFORMANCE WITH REAL-TIME FEEDBACK

Clinical Decision Support

Clinical decision support (CDS) has been defined as a system that uses two or more items of patient data to generate case-specific advice [7]. In practical terms, CDS includes a wide range of functions, including predefined rules, alerts, reminders, workflow, and collaboration tools—and associated content—for improved medical decision making. CDS is often intended to facilitate the introduction of and conformance to evolving evidence-based medical protocols and standards of care while enabling appropriate individual physician discretion (such as during order entry). Rules are, at their core, built on IF/THEN logic statements that allow a tremendous amount of flexibility and power to be added to systems within critical care and across the hospital or integrated health system.

Over the past decade, the business end (e.g., the user experience) of CDS has been the alert box. A growing number of studies are beginning to reveal the critical limitation of alerts that, by design, interrupt the clinician's workflow, in particular, during order entry [8,9]. The primary reason for this limitation lies in CDS systems designed mainly to alert post hoc after the clinician has requested a particular item (e.g., drug dosage, test).

CDS has the potential to provide special value in settings like the ICU due to the density of data assailing the busy critical care physician and the ability of computers to combine, synthesize, and correlate these data and then create more complex rules and information interpretation displays [10]. Studies have demonstrated that critical care rounds may challenge the physician with 20 times more data elements than the human brain can simultaneously process [11]. In the past, we have relied on the team approach to cope with this onslaught. In the current practice reality of competing priorities of intensivist time, numerous handoffs among providers, the need for IT to take more of a facilitation role for the ICU physician and

nurse is substantial. The next emerging developments in CCIS are likely to be in both the areas of visual design and complex rules and algorithms to predict and inform clinicians about patient circumstances by multiple means. This is discussed, along with emerging techniques for ICU performance management and related metrics, in a later section of this chapter.

Stepwise Plan of Implementation of a Critical Care Information System

The following steps enable the physician, in combination with other stakeholders such as nurses and pharmacists, to evaluate, select, and obtain maximal benefits from CCIS systems, with the assistance of a professionally certified and experienced project manager (typically from the IT department). It is the project manager who coordinates overall project planning, ensures that the required technical resources will be available on time, and monitors tasks and milestones among the project team. Technical needs such as interfaces to other IT systems and to medical devices, hardware, power, physical space, network access, and system security are necessary parts of this coordinated planning in addition to software delivery and configuration.

1. Goal setting: Considerations for valued, realistic goals. Experience has shown that the most important goal for achieving successful CCIS implementation is improvement in the quality of patient care. An ICU team is well versed in the concept of change, usually in the context of changes in patient condition. However, deploying and leveraging a CCIS implementation is a different kind of change. It should enable and will require reengineering of certain processes and a reduction in productivity during transition should be anticipated. An ICU team is not expected to tolerate delays in patient care, and needs to plan carefully and set realistic expectations around workflow issues that typically occur in the context of the learning curve necessary to use a new CCIS. With the goal of improved quality of patient care as the guiding light, the sequence of introduction of CCIS and the speed of implementation can be considered. An improved structure of order sets that have the support of virtually all clinicians and that interface with other department's systems (e.g., laboratory, pharmacy, radiology) is key [12].
2. CCIS users must have understanding and input into CCIS design before implementation. The history of CCIS implementation has shown that physicians are the most likely group to be surprised by CCIS structure and function. Reasons include lack of physician attendance at planning meetings, and therefore little direct input in CCIS planning and configuration, due to physician perception of systems as being solely clerical. The importance of involving clinically influential physician leaders in a successful CCIS process has been shown in the literature [21]. The chief medical informatics officer (CMIO), serving as a bridge between physicians and IT through design, training, support, and enhancement, improves clinical IT deployments. Note that about 7% of CMIOs come from the ranks of intensive care medicine, according to recent survey data [13].
3. Preemptive workflow and practice reengineering. The knowledge base necessary for a successful CCIS implementation is not limited to learning about the system itself. More important is the timely recognition that the workflow changes engendered by implementation can be both tolerated and supportive of the central goal of improved patient care.
4. Minimize changes to base system before implementation. This step is really a caveat of step 2. Yes, users should have some time to learn the out-of-the-box system and suggest changes before implementation, but that has to be balanced with the actual experience of the "shake-down cruise" period with the new system during the daily operations of the ICU. Veteran computer analysts of many CCIS implementations will attest to the frequency of changes of some components of a system back to factory specs after a few weeks or months of use. Nothing can replace time and experience in using a system in the actual ICU environment to truly recognize what would or would not be a helpful modification.
5. Establish implementation milestones. Implementation of a complex system should be phased in gradually, with each step building on the foundation of the previous component. Starting with results reporting, to computerized physician order entry (CPOE), then to decision support, workflow is increasingly affected and the changes take time to be absorbed effectively. This process is necessary to avoid any adverse impact on the all-important central goal of improved patient care.
6. Establish a backup/back-out plan for each milestone. It needs to be recognized that a successful implementation may require some temporary delays for extra training or system reconfiguration. Daily clinical operations of the ICU must always be paramount.
7. CCIS should be viewed as a system of patient-centered reminders, not an attempt to control providers. CCIS systems should be a helpful aid in optimizing patient care; for example, memory aids and consistent care reminders can be helpful. Components that may be perceived as attempting to control user behavior are not well accepted, and systems have been rejected on these grounds [14].

Critical Care Specific Technologies

Concurrent Process Monitoring

On the most basic level, CCIS put an end to juggling the awkwardly large flow sheet. Like CPOE, they eliminate the confusion and potential errors that can result from illegible handwriting and from fluid contamination, including the familiar coffee spill. The truly significant contributions CCIS makes to patient safety are in the areas of care processes and medical decision making. First among these is the ease of access to data. Access to a paper record can be problematic in the ICU, where multiple clinicians need to assess the patient's clinical condition and response to treatment. Electronic records allow multiple caregivers to view the data at the same time, without waiting to access the one-and-only paper chart. Clinicians not in the ICU can check on a patient's status without physically having to be in the unit, allowing them to be consulted at the very moment their expertise is needed. When timeliness is critical, access is a critical enabler.

The impact of access on patient safety is enhanced when clinicians have confidence that the data provided are accurate and timely. By automating calculations, CCIS ensures that measures such as input/output are computed correctly, and provides multiple measures, including those too time-consuming to compute routinely on paper such as hemodynamic calculations incorporating many variables. In addition, CCIS can automatically acquire data directly from monitoring equipment and ventilators, eliminating delays and errors in data gathering.

Unlike the paper flow sheet, with its fixed format, CCIS offer multiple displays of data. Each display provides a problem-oriented view suitable for analysis of the issue at hand. Constrained to one view of the data, physicians using paper-based systems on occasion resort to duplicate data entry, a practice nurses are trained to disallow. By contrast, CCIS allows

the clinician to select from multiple displays, each providing a problem-oriented view suitable for analysis of the issue at hand.

CCIS further supports the clinician by easing trend recognition. Specific displays establish the correlation of events in time, offsetting the possibility that it might be less apparent on the computer screen than on the paper flow sheet. Other displays provide multi-day views, which are critical for measures like fluid balance and fever curves, surpassing the paper flow sheet's view of only one day at a time. The displays on CCIS integrate multiple data elements that stand in isolation on the existing flow sheet. By combining vital signs, laboratory results, ventilator settings, medication drips, and medication administration, CCIS enables clinicians to address the complicated clinical scenarios characteristic of critically ill patients in ICUs. This integrated record also assures attention to details that can be lost in a frenetic setting; for example, by issuing a warning that a medication is overdue or being dosed earlier than appropriate per orders.

In the ICU and throughout the hospital, specialized tools can address "failure to rescue," which has been identified by the Agency for Healthcare Research and Quality (AHRQ) as accounting for the majority of patient-safety Medicare deaths. These tools provide proactive clinical surveillance; they interpret patient data (which are collected by the CCIS) and act as early warning systems.

In failure to rescue, the patient experiences clinical decompensation over a period of hours, without intervention by caregivers. This error of omission occurs for any of several reasons. The changes in the patient's condition may be subtle; for example, a physiologic value may be decreased, but not alarmingly so unless viewed as part of a trend. In other cases, changes may not be appreciated for what they signify. Clinicians may lack the necessary expertise to discern such changes or may be overwhelmed with other tasks. Indeed, according to the AHRQ, there is strong evidence that level of staffing and the nursing skill-mix are both factors in this failure.

Delays in detecting changes are of grave concern for a simple reason: the earlier the intervention, the greater the likelihood for a better clinical outcome. Intervening at the first signs of decompensation may make it possible to avert cardiorespiratory renal failure or address a more treatable complication. For example, stabilizing a patient whose heart rate is reaching dangerous levels (less than 40, more than 130 beats per minute) is more likely to succeed and less likely to involve additional complications than resuscitating a patient in a state of cardiac arrest.

There are warnings, if caregivers are able to recognize critical data among the numerous data elements on every patient. Studies of clinical instability suggest that patients experience symptoms in advance of critical events like cardiac arrest. In one study, 70% showed evidence of respiratory deterioration within 8 hours of arrest; in another, 66% of patients showed abnormal signs and symptoms within 6 hours [15].

Proactive clinical surveillance systems highlight trends and out-of-bounds values and conditions for further scrutiny. They provide displays—"dashboards"—that integrate different data elements to optimize evaluation of clinical problems. An additional feature offers severity scoring for the purpose of early detection of decompensation, issuing modified early warning scores to alert clinicians to problems as they develop.

These dashboards function both inside and outside the ICU to identify patients whose conditions are worsening, putting them in critical condition. Depending on their resources, hospitals may respond in several different ways.

In many hospitals, ICUs are staffed with nurse specialists and have high nurse-to-patient ratios. Yet most hospitals in the United States do not have a full-time intensivist on staff, ready to step in when a patient decompensates in the ICU or in another unit elsewhere in the hospital. In some instances, physicians in other specialties who practice in the ICU choose not to have an intensivist on staff, even if their hospital has the financial resources to recruit one. Nationally, there are more ICUs than intensivists. In 2001, staffing every ICU sufficiently would have required 35,000 to 40,000 intensivists, and there were less than 10,000 of these specialists.

Outside critical care areas, nurse-to-patient ratios are typically lower. Moreover, general medical/surgical areas are staffed by nurses who are not trained in the care of the critically ill. When a patient decompensates, the nurse is less likely to recognize this has happened, and the patient is less likely to receive appropriate interventions. Failure to recognize and respond quickly to patients with deteriorating conditions not only results in cardiac arrests and death, but is also associated with serious complications and prolongation of hospital length of stay. For patients and professionals in these units, the dashboards provided by hospital-wide proactive clinical surveillance systems improve safety, if in fact there is a mechanism for responding.

One approach is to create what the Institute for Healthcare Improvement [16] calls a rapid response team (RRT), also known as medical emergency team. The RRT consists of clinicians and nurses with critical care expertise that can be called anywhere in the hospital if a patient experiences acute change(s) in physiologic conditions; for example, in respiratory rate (more than 8 or less than 28 per minute), systolic blood pressure (less than 90), oxygenation, and neurologic status. As structured by the Institute for Healthcare Improvement, the program is contingent on a nurse to request help.

Whether or not a hospital has RRTs, a computerized surveillance system could function to alert clinicians that a patient is decompensating. Studies show a 50% reduction in non-ICU cardiac arrests, reduced postoperative emergency ICU transfers (58%) and deaths (37%), and reduction in arrest prior to ICU transfer (4% vs. 30%). With RRTs, one 750-bed community hospital reported a 23% decrease in their overall code rate per 1,000 discharges, a 44% decrease in codes occurring outside their ICU, and a 48% increase in the percentage of coded patients surviving at discharge.

Whether or not a hospital has RRTs, surveillance systems function to alert clinicians that a patient is decompensating. In either situation, the decision may be made to move the patient to critical care. Survival in the ICU is enhanced if patients are brought to the ICU in less critical condition and are less likely to experience severe complications. Moving patients into the ICU reduces the incidence of codes in areas outside the ICU that are less skilled at responding to them. Effective patient triage, management of potentially seriously ill patients prior to development of progressive physiologic deterioration, and reduction of unanticipated ICU admissions may also result in savings that can neutralize the cost of maintaining an RRT.

Another capability provided by CCIS that has the potential to improve patient safety includes concurrent process monitoring. This relies on details of care that define how a process is being implemented. When data are captured electronically and stored as discrete data elements, they can become available for analysis. When analyses are concurrent (e.g., done as care is delivered), they allow managers and caregivers to have visibility into global processes of care. In the ICU, concurrent process monitoring allows evaluation of whether a particular practice is actually being implemented and whether it is affecting outcomes, such as elevation of the head of the bed to reduce the likelihood of VAP.

Historically, organizations are good at creating policies and procedures, but much less effective in deploying them. Although it is easy to sit in a conference room and discuss them, it is harder to get people to follow them. If data are extracted

and tabulated manually, it is laborious to figure out whether a particular practice is being implemented and the reporting is done long after the events being studied have occurred. In such cases, caregivers may believe "It used to be that bad, but now we're better." With more retrospective analysis, the same pattern repeats.

In contrast, concurrent process analyses allow the implementation of evidence-based practices by identifying and reinforcing practice patterns as they occur. Moreover, concurrent monitoring takes advantage of data already being gathered in the course of care, eliminating the need for duplicate data entry or chart abstraction.

Critical Care Decision Support Systems

The ICU is routinely acknowledged by hospital executives as a high-cost, high-risk hospital center. Intensive care and the role of intensive care-trained professional have been far less well appreciated as the service that often is the difference between effective and profitable hospital care for seriously ill patients. Ironically, despite great challenges of data collection and a general lack of payer and care-delivery organization support, ICU researchers have been among the real pioneers in trying to understand how to impact the effectiveness and efficiency of ICU and overall hospital care. As clinical automation and the resulting routine and standardized data collection are becoming more common, it is likely that these important methods for measuring, comparing, and improving care will find their way into mainstream medical practice.

ICU PERFORMANCE MANAGEMENT

Since the Institute of Medicine published its 1999 "expose" on patient safety [17], the ICU has received increased national attention as an important target for medical error reduction and improved quality. Both the Leapfrog Group collaborative of large employers and the Joint Commission accreditation organization have focused on developing national ICU performance measurement metrics [18]. IT can be used to more easily gather patient, process, and outcomes data and facilitate improvement. Performance measures are typically categorized as structural (how care is organized), process (what is done), or outcomes (including medical/functional, such as death or the ability to perform specific functions of daily life); experiential, which covers both patients/families and providers; and financial, which includes both cost/resource use and profitability perspectives.

Structure and process measures are used on the presumption that their variance causes a specific significant variance in one or more outcomes. Examples of popular structural ICU measurable processes are intensivist coverage [19] and appropriate levels of nurse staffing. Head-of-bed elevation in mechanically ventilated patients to prevent nosocomial pneumonia and associated increased mortality is an example of a contemporary measurable process [12].

One of the most significant challenges in quality improvement efforts is the lack of trust or alignment that can exist among clinicians, hospital administrators, insurance companies, and government over the motivation behind measurement. Clinicians believe that the purpose of measurement should be to understand and improve—while they too often, and too often rightly, assume payers' and overseers' plan to use metrics only to judge and to penalize—not to reward superior performance or improve patient care but only to drive down cost.

Given this environment, without standardized measures of meaningful medical outcomes that are defined, understood, and accepted by the relevant clinical community, making significant progress is difficult. Business intelligence systems, including performance dashboard techniques, that combine clinical data from computer-based patient records with financial data for analysis and reporting are predicted to be an area of increased interest. As this evolution occurs, critical care leaders will want to assure that their unique information needs are met in these systems and that appropriate attention is given to elements like risk adjustment and critical care-specific process analysis. Niche ICU analytic systems such as the Virtual Pediatric Intensive Care Unit (PICU) Performance System/National Association of Children's Hospitals and Related Institutions, the Vermont-Oxford Network for neonatal intensive care, and Cerner Corporation's Acute Physiology, Age, Chronic Health Evaluation (APACHE) prognostic, concurrent, and retrospective decision support system focused on adult ICU units are also available [20].

RISK-ADJUSTMENT MODELS FOR COMPARING INTENSIVE CARE OUTCOMES

Risk adjustment, severity adjustment, or case-mix adjustment are terms used to describe mathematical models derived from large datasets of a particular population whose purpose is to represent the relative risks individual patients bring at the entry point to care process. Patient risk factors of course impact what care processes and resources are required to produce similar outcomes and what the best realistically achievable outcomes are. Modeling research needs to define three elements: (a) the binary or continuous outcome variable(s) to be modeled (e.g., lived/died, length of stay), (b) the beginning and end points in time (e.g., at admission to the ICU, at discharge from the hospital, at 100 days), and (c) the specific risk factors to be included (e.g., age/gestational age, weight/birth weight, diagnosis, physiology). Because most hospital patient records are still paper-based, the most viable data source developing risk adjustment has been those using administrative (claims) data, examples being APR-DRGs (all patient refined diagnosis-related groups) and disease staging. Model developers juggle the collection cost versus the desirability of capturing specific data, but unequivocally more detailed patient data than that included in claims is required to adequately represent patient-risk variance in the ICU population. Model developers also struggle with defining reasonable end points for capturing outcomes. They also need to consider and factor in relationships among institutions and settings, potentially "gaming of the system." A report card that inadequately adjusts for patient risk might harm hospitals and physicians who take on the highest risk patients, or encourage entities to transfer dying patients to reduce their mortality [20]. As an example, a recent analysis of several Pennsylvania hospitals pointed out a facility with higher reported stroke mortality rates, in part because it kept more terminal stroke patients in the hospital rather than discharging them to home or hospice [22]. As Iezonni [23] notes, "developing risk adjusters de novo is complicated and often frustrating." Risk models for adult, pediatric, and neonatal ICU populations have been sufficiently vetted and have sufficiently evolved to serve as the foundation for nationally standardized outcomes measurement in an increasingly automated hospital environment. Risk models need to be reevaluated periodically to assure that they remain consistent with current patient factor, care process improvements, and outcomes' experience. They should also be evaluated for their appropriateness in geographies not included in their modeling datasets.

There are multiple risk-adjustment models in current use. Representative examples of ICU risk-adjustment models based primarily on U.S. patient data include

1. APACHE IV (Acute Physiology, Age, Chronic Health Evaluation, 4th version) [24,25]
2. PRISM (Pediatric Risk of Mortality) [26]
3. SNAP/SNAPPE (Score for Neonatal Acute Physiology) [27]
4. Neonatal Risk Models of the Vermont-Oxford Network

EVALUATING RISK-ADJUSTED OUTCOMES INFORMATION

Because risk-adjusted assessments are based on mathematical models, taking an objective approach to understanding the causes of variance data is logical. For example, there are four main causes of variance, and sequentially evaluating them helps clinicians gain familiarity with the models and acceptance of variance between actual and predicted results. These models include (i) data randomness (small sample), (ii) existence of patient risk factors not incorporated or (iii) adequately weighted in the particular model, and (iv) variance likely attributable to differences in care.

Emerging Trends: Predictive Modeling and Data Visualization

Predictive analytics enable an organization to estimate or anticipate the risk of future events, and are used increasingly in other industries, such as for predicting consumer behavior. In health care, these techniques are often applied for planning demand for healthcare services and facilities, for identification of at-risk populations, and for actuarial projection of healthcare utilization or life span.

Clinical decision support systems in the future will take more advantage of larger databases of increasingly granular patient data to drive pattern recognition engines that will help clinicians predict physiologic deterioration progressively earlier in its course. Examples of predictive models in use today include the individual patient predictions components of the APACHE IV ICU models referenced previously [25], and the Northern New England Cardiovascular Disease Study Group's preoperative mortality risk and cerebrovascular accident and risk of vascular complication models [28]. Not intended to replace but to support physician judgment, such predictive models have to date focused on evaluating the appropriateness of ICU admission and readiness for discharge, assessing patient progress and effectiveness of current therapies, building care team consensus around prognosis and care strategies, identifying patients for palliative care assessments, and improving

Unit Abbreviation	[redacted]-CV						
Unit Name	CV Surgery						
Medical Director	[redacted], MD						
Nursing Director	[redacted], RN						
	December	**November**	**October**	**6 Month Avg**	**12 Month Avg**	**Current vs. 12-mo Trend**	**Notes**
Operating Beds	8.0	8.0	8.0	8.0	8.0	No Change (<1%)	
Discharges	47.0	54.0	50.0	47.0	47.4	No Change (<1%)	
Occupancy	62.6%	65.9%	62.6%	58.2%	62.4%	No Change (<1%)	
Average ICU Length of Stay (days)	3.30	2.93	3.11	3.04	3.20	Increase of 3.1%	
Average Hospital Length of Stay (days)	5.30	5.19	5.58	5.01	5.44	Decrease of 2.5%	
% IMU/Routine Room Charges	24.2%	18.9%	19.0%	17.2%	16.0%	Increase of 51%	
ICU Glucose Monitoring							
Bedside glucose measurements per day	5.79	6.84	3.54	4.20	3.54	Increase of 63.7%	All measurements
Euglycemia (80-150 mg/dL)	78.0%	73.6%	69.0%	68.3%	56.5%	Increase of 38%	Only post-24-hour samples
Hypoglycemia <60 mg/dL	0.9%	1.4%	0.5%	1.1%	0.9%	Decrease of 2.1%	Excludes first 24 hrs
60-79 mg/dL	6.1%	5.0%	3.7%	4.4%	3.1%	Increase of 98.4%	Excludes first 24 hrs
Euglycemia 80-150 mg/dL	78.0%	73.6%	69.0%	68.3%	56.5%	Increase of 38%	Excludes first 24 hrs
Hyperglycemia >150 mg/dL	15.1%	59.1%	68.3%	63.1%	74.2%	Decrease of 79.7%	Excludes first 24 hrs
ICU HAI Bundle Compliance							
VAP Bundle Compliance - MD	NA	100.0%	100.0%	100.0%	100.0%	-	
VAP Bundle Compliance - Nursing	NA	100.0%	0.0%	50.0%	33.3%	-	
CR-BSI Insertion Bundle Compliance	100.0%	90.0%	92.3%	97.1%	97.3%	Increase of 2.8%	
CR-BSI Line Maintenance Compliance	100.0%	44.4%	25.0%	47.7%	51.4%	Increase of 94.6%	
ICU Utilization							
Epotin cost per ICU day	$0.00	$2.17	$2.95	$1.74	$1.60	Decrease of 100%	Procrit & Aranesp for non-ESRD
Nicardipine cost per ICU day	$5.93	$3.39	$6.91	$5.29	$9.25	Decrease of 35.9%	Cardene only
Propofol cost per ventilator day	$4.92	$9.69	$13.15	$9.49	$8.42	Decrease of 41.6%	
Antibiotics cost per day	$20.97	$44.71	$37.38	$35.31	$30.39	Decrease of 31%	
Average # Ventilator Days	1.62	2.67	2.89	2.27	2.10	Decrease of 22.9%	For ventilated patients only
Vent-to-Trach Days	0.00	0.00	0.00	0.00	10.00	Decrease of 100%	Excludes same-day trachs
% Avoidable ICU Days	0.0%	0.0%	0.0%	0.0%	0.0%	-	*Subject to reporting revision*
ICU Costs & Margin							
Total Indirect cost per patient day	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	Increase of 53.7%	
Total Direct cost per Patient day	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	Decrease of 7.5%	
Laboratory	$306	$325	$340	$361	$350	Decrease of 12.7%	
Chargeable Supplies	$1,621	$1,804	$1,667	$1,790	$1,774	Decrease of 8.6%	
Pharmacy	$305	$383	$334	$357	$315	Decrease of 3.4%	
Radiology	$30	$28	$32	$30	$29	Increase of 5.4%	
Respiratory	$30	$44	$42	$37	$37	Decrease of 19.4%	
Room & Other	$1,370	$1,474	$1,340	$1,438	$1,454	Decrease of 5.8%	
Contribution Margin per ICU Case[1]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	Increase of 42.8%	
ICU Outcomes							
% Readmissions	0.0%	4.0%	2.0%	2.1%	2.6%	Decrease of 100%	
Within 48 hrs leaving ICU	0.0%	4.0%	0.0%	0.7%	1.8%	Decrease of 100%	
After 48 hrs leaving ICU	0.0%	0.0%	2.0%	1.4%	0.9%	Decrease of 100%	
% Mortality	0.0%	1.9%	0.0%	2.1%	1.9%	Decrease of 100%	
High Risk[2] (APR-DRG)	NA	1.9%	0.0%	2.1%	1.8%	-	APR-DRG ROM = 3 or 4
Low Risk[2] (APR-DRG)	NA	0.0%	0.0%	0.0%	0.2%		APR-DRG ROM = 1 or 2

FIGURE 209.1. ICU metrics dashboard. Courtesy of Memorial Hermann Healthcare System, Houston, Texas.

communications and setting realistic expectations with patients and families. Additional efforts now underway include a database being developed at the Mayo Clinic that incorporates clinical patient data along with genomic data. The expectation is that powerful prediction models will result from analysis of this large-scale aggregated patient history, outcomes, and genomic dataset [29].

Another large-scale database is currently being collected and analyzed by a collaborative of industrial, medical, and academic partners (MIT, Philips Medical Systems, and the Beth Israel Deaconess Medical Center) [30]. To date analysis of this dataset (MIMIC II) has resulted in several prediction models that provide a rudimentary "early warning system" for several specific types of physiologic deterioration. One such model consists of a rule set that, when applied to near real-time patient physiologic data, is capable of predicting hemodynamic deterioration hours before its occurrence [31]. Early warning alerts from advanced clinical decision support systems hold the promise of improving response times to patient events. Although it seems to logically follow that such early identification of physiologic deterioration would allow earlier intervention and prevention of patient crises, the effects of these interventions on patient outcomes are yet to be studied.

It is important to note that the use of individual patient risk prediction for concurrent or prospective decision support has been challenging to incorporate into physicians' workflow, and has struggled to obtain widespread physician acceptance.

ADVANCES IN DATA VISUALIZATION TECHNIQUES

Although many organizations have successfully applied performance metrics, severity scores, and predictive risk models for improved quality and decision making, data collection/calculation and integrated display is likely to expand more in the next decade than in all previous ones. Designers have much work to do to accomplish meaningful display of the most important patient, process, alerting, and predictive information without overloading the clinician's ability to absorb and respond. Two examples of the application of modern data visualization techniques are represented in Figures 209.1 and 209.2. Figure 209.1 illustrates a comprehensive ICU performance management dashboard, as used by the Memorial Hermann Healthcare System in Houston, Texas. Note the integration of different categories of metrics, such as census, occupancy, glycemic control, infection prevention bundle compliance, medication and ventilator utilization, financial data, and patient outcomes. This is a fully automated monthly report that is electronically distributed to ICU and executive management across the health system. Figure 209.2 displays a comprehensive real-time ICU hospital-acquired infection (HAI) dashboard, including HAI rates and detailed bundle compliance results for prevention of catheter-related blood stream infection and VAP. This is a live intranet web display that is

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Hospital Acquired Infection Indicators

MEMORIAL HERMANN

Return to Daily Flash
Core Measures
Patient Safety Indicators
Hospital Acquired Infection Indicators
Ambulatory Measures
TJC AMP Online Documentation
Personnel

Date: Aug 26, 2009

Balance Scorecard Core Measures

View Facility: [redacted] Hospital - Adult

Monthly Measurements

	Jul 09	Jun 09	May 09	Apr 09	Mar 09	Feb 09	Jan 09	Dec 08	Nov 08	Oct 08	Sep 08	Aug 08
HAI Infection Rates												
Catheter-Related Blood Stream Infection	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.22	0.00	4.17
Ventilator-Associated Pneumonia	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Surgical Site Infection	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hospital-Acquired Infection Roll-Up	INC	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.22	0.00	4.17
CY09 Surgical Site Infection		0.00	0.00	0.00	0.00	0.00	0.00					
Surgical Site Infection												
Blood Stream Infection Prevention Bundle												
Central Line Insertion												
MD Hand Hygiene	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Chlorhexadine	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
MD gown, gloves, hat & mask	98.70%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Drape patient head to toe	98.70%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Sterile field maintained during procedure	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Assistant Hand Hygiene	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Assistant gown, gloves, hat & mask	100.00%	98.18%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Insertion Bundle Compliance	98.70%	98.18%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
% Femoral Lines	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.72%	0.00%	0.00%	0.00%	0.00%
% Femoral Lines justified by careful site selection								0.00%				
Audit Compliance												
# Audits completed	77	55	81	59	91	81	23	58	97	89	39	60
#CVC Insertions												
Audit Compliance rate												
Central Line Maintenance Bundle												
MD Line "Necessity" documented daily	100.00%	75.44%	72.22%	82.35%	61.82%	64.29%	53.85%	50.00%	78.95%	90.00%	100.00%	100.00%
CVC dressing occlusive & intact	100.00%	94.74%	100.00%	100.00%	96.36%	85.71%	84.62%	100.00%	100.00%	95.00%	100.00%	100.00%
Site healthy w/o redness or drainage	100.00%	94.74%	100.00%	100.00%	100.00%	96.43%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Dressing change <7 days for transparent or <2 days for gauze	100.00%	98.25%	100.00%	91.18%	94.55%	78.57%	84.62%	75.00%	100.00%	90.00%	100.00%	90.91%
All CVC tubing labeled w/ date & time	100.00%	96.49%	100.00%	100.00%	92.73%	96.43%	69.23%	100.00%	94.74%	100.00%	100.00%	90.91%
All CVC tubing dates compliant w/ policy	100.00%	96.49%	100.00%	100.00%	98.18%	96.43%	76.92%	100.00%	100.00%	95.00%	100.00%	100.00%
All CVC lines labeled w/ date & time of insertion	95.24%	89.47%	94.44%	88.24%	89.09%	71.43%	53.85%	50.00%	100.00%	90.00%	100.00%	90.91%
Nursing Bundle Compliance	95.24%	82.46%	94.44%	82.35%	83.64%	53.57%	46.15%	50.00%	94.74%	75.00%	100.00%	90.91%
Maintenance Bundle Compliance	95.24%	68.42%	66.67%	73.53%	54.55%	39.29%	38.46%	50.00%	78.95%	75.00%	100.00%	90.91%

FIGURE 209.2. Hospital-acquired infection indicators dashboard. Courtesy of Memorial Hermann Healthcare System, Houston, Texas.

updated constantly. Both reports are widely available within the Memorial Hermann system and have helped drive performance excellence.

Most importantly, to taking advantage of these new possibilities, though, is that senior medical executives, ICU directors, and clinicians must "own" responsibility for localizing and embracing performance metrics and the advancing base of evidence-based decision support being made available.

In conclusion, the modern CCIS is a dynamic information instrument, extending the capabilities of the intensive care physician and staff in ways that would be considered science fiction only a generation ago. The rapid adoption of these new information tools is now anticipated, as the complexity of medical care, particularly in the ICU setting, becomes increasingly demanding and evidence-based decision making moves from a goal to an expectation of acute medical care.

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CHAPTER 210 ■ DEFINING AND MEASURING PATIENT SAFETY IN THE CRITICAL CARE UNIT

ALAN M. FEIN, STEVEN Y. CHANG, SARA L. MERWIN, DAVID OST AND JOHN E. HEFFNER

Patient safety has become a major concern of the general public, policy makers, and local, state, and national government. Frequent news coverage has been devoted to individuals who were victims of serious medical errors. In the 1999 publication of the Institute of Medicine, *To Err Is Human: Building a Safer Health Care System* [1], the risks of medical care were highlighted, particularly the nearly 100,000 deaths per year that could be attributed to medical errors. A general sense of the importance of a safety culture in the intensive care unit (ICU) is increasing, as suggested by the multiple reports and publications in the lay and scientific media devoted to this topic [2].

The high-risk environment of the ICU benefits from integrated and coordinated systems that identify patient safety problems and report them to providers so they can improve

their performance. To maintain high-quality care, critical care teams need to know not only what to do but also how they are doing and what they need to do to improve their structure, processes, and outcomes of care. Donabedian [3] first described these three domains—structure, process, and outcome—as necessary elements for measuring the quality of health care. They also serve as a conceptual framework for measuring patient safety in the ICU.

On a broad scale, ICU patient safety-reporting systems identify trends and patterns allowing health care organizations, governmental agencies, and private accreditation organizations to monitor the quality and safety of health care delivery, which facilitates public reporting of data and increases transparency [4]. Patient safety-reporting systems also have the potential to create large data repositories that inform the development of strategies that reduce the risk of preventable medical incidents [5,6].

Effective reporting systems require definitions and methods that are standardized throughout the community of providers, so that information can be shared and meaningful comparisons can be made. In the 2003 report, *Patient Safety: Achieving a New Standard of Care,* the Institute of Medicine (IOM) emphasized the importance of standardizing and better managing information on patient safety to improve outcomes of care [5]. A critical element of this standardization is the development of a common taxonomy of patient safety terms. In the absence of standardized terminology, health care providers have no way to know what events to capture and how to describe those events in consolidated reports [7]. Also, fragmented approaches for defining and classifying near misses, adverse events, and other patient safety concepts prevent aggregation of data in formats that allow analysis and summary reporting [1,8]. To date, governmental and private sector accrediting bodies have not coordinated their efforts to develop actionable, integrated, validated, and reliable systems to measure and report medical errors and patient safety [9].

SAFETY LESSONS FROM OTHER INDUSTRIES

Safety and error prevention in the health care setting compares unfavorably with that in aviation, banking, chemical manufacturing, and military services in peacetime. Lessons from these industries are now being applied to the health care industry. Approaches to safety in these industries are characterized by well-defined strategies to protect workers and customers. Technology-based approaches are part of this strategy, but organizational and psychologic aspects are contributing factors as well. For example, developing a culture of safety has been identified as one important method of improving safety. The aviation industry has focused on the importance of teamwork in reinforcing a safety culture.

Although technical, organizational, and psychologic interventions are effective, it is also worth noting the limits of the existing method. Persistence of fatalities in aviation and auto transportation suggest that safety efforts may be counterbalanced by other competing risk factors such as high volumes, greater complexity of the product, cost-pressure, and rapidly changing designs. This is particularly relevant to health care because the population is changing (higher number of increasingly older and higher-risk patients) and the technology is changing at a very rapid rate [10].

Thus, there is probably an upper limit in terms of cost-effective health care safety that can be reached, but has not been attained. Health services are being encouraged by the IOM report to aim for an error rate of less than 3.4 per million, that is, "six-sigma quality." The discipline of anesthesiology in particular has made substantial contributions through its development of a safety culture and equipment-manufacturing standardization that resulted in a reduction in anesthesia-related deaths to 4.4 per million, that is, "five-sigma standard."

To achieve this standard in the ICU, there must be a precise definition of the terms needed to study patient safety, their methods of measurement, how these can be applied to the special problems of ICU organization, physician training, and development of a culture of safety, and finally how these concepts apply to governmental regulations.

DEFINITIONS

The basic terms in common use to define concepts of patient safety are listed in Table 210.1 and show the working definitions that have entered into the lexicon of the patient safety industry [11]. Health care quality is defined by the IOM as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [12]. This definition conforms to two (process and outcome) of the three constructs (structure, process, and outcome) proposed by Donabedian [3] to be necessary for measuring the quality of health care. The IOM has also listed several attributes of quality care that define quality care as being safe, patient-centered, timely, effective, efficient, and equitable [13]. Thus, patient safety is one domain within the broader concept of quality.

Patient safety has been variously defined by the Agency for Health Care Research and Quality (AHRQ) as "the absence of the potential for, or the occurrence of, healthcare associated injury to patients created by avoiding medical errors as well as taking action to prevent errors from causing injury" [14] and "freedom from accidental or preventable injuries produced by medical care" [15].

Within this context of safety, medical errors are defined as "mistakes made in the process of care that result in or have the potential to result in harm to patients. Mistakes include the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. These can be the result of an action that is taken (error of commission) or an action that is not taken (error of omission)" [14]. Errors of commission (e.g., ordering an incorrect drug dose) as compared with errors of omission (e.g., failure to order heparin for venous thromboembolism prophylaxis) are more readily noted. Errors are further classified as *active* or *latent* [16,17]. Active errors occur at the interface between a human provider and a care-delivery system (e.g., mechanical ventilator, intravenous pump) and typically involve readily apparent actions (e.g., adjusting a dial incorrectly). Latent errors define a less obvious failure of a health care organization or structure that contributed to errors or allowed the errors to harm patients. An example of a latent error would be understaffing of nurses in an ICU. Other typologies include domains that ascribe characteristics of preventability, seriousness and whether the error was intercepted before affecting a patient [18] (Table 210.1).

Errors have also been classified as *slips* or *mistakes*. Slips are failures of automatic behaviors, or lapses in concentration (e.g., forgetting to perform a routine task due to a lapse in memory) and often occur from fatigue or distractions in the workplace. Mistakes represent incorrect choices, such as choosing the wrong drug for a clinical condition, and typically result from inexperience or lack of knowledge or training. The remedies for these two types of errors differ, with slips being more responsive to removing distractions from the workplace or automating monotonous tasks and mistakes respond to increased training or supervision.

Incidents are defined as unexpected or unanticipated events or circumstances not consistent with the routine care of a particular patient, which could have or did lead to an unintended

TABLE 210.1

GENERAL TERMS USED IN PATIENT SAFETY

Quality: The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge

Patient safety: The absence of the potential for, or the occurrence of, health care-associated injury to patients created by avoiding medical errors as well as taking action to prevent errors from causing injury. Freedom from accidental or preventable injuries produced by medical care

Medical errors: Mistakes made in the process of care that result in or have the potential to result in harm to patients. Mistakes include the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. These can be the result of an action that is taken (error of commission) or an action that is not taken (error of omission)

Active errors: Errors that occur at the interface between a human provider and a care-delivery system (e.g., mechanical ventilator, intravenous pump) and typically involve readily apparent actions (e.g., adjusting a dial incorrectly).

Latent errors: Less obvious failures of a health care organization or structure that contributed to errors or allowed the errors to harm patients. An example of a latent error would be understaffing of nurses in an intensive care unit.

Serious medical errors: A medical error that causes harm (or injury) or has the potential to cause harm. Includes preventable adverse events, intercepted serious errors, and nonintercepted serious errors. Does not include trivial errors with little or no potential for harm or nonpreventable adverse events.

Intercepted serious error: A serious medical error that is caught before reaching the patient

Nonintercepted serious error: A serious medical error that is not caught and therefore reaches the patient but because of good fortune or because the patient had sufficient reserves to buffer the error, it did not cause clinically detectable harm

Nonpreventable adverse event: Unavoidable injury due to appropriate medical care

Preventable adverse event: Injury due to a nonintercepted serious error in medical care.

Slips: Failures of automatic behaviors, or lapses in concentration (e.g., forgetting to perform a routine task due to a lapse in memory) and often occur from fatigue or distractions in the workplace.

Mistakes: Incorrect choices, such as choosing the wrong drug, a clinical condition and typically result from inexperience or lack of knowledge or training.

Incident: An event or circumstance that could have, or did lead to, unintended and/or unnecessary harm to a person.

Harm: Death, injury, suffering, dissatisfaction, or disability experienced by a person.

Near miss: Any incident that could potentially lead to patient harm.

Adverse event: Any injury due to medical management, rather than the underlying disease.

Adapted from references [11,12,14–18].

or unnecessary harm to a person, or a complaint, loss, or damage. Adverse events are different, and are defined as an "untoward and usually unanticipated outcome that occurs in association with health care" [14] or more broadly stated by the IOM as "an injury resulting from a medical intervention" [1]. The Critical Care Safety Study defines adverse events as "Any injury due to medical management, rather than the underlying disease [18]. Describing an event as an adverse event does not imply poor-quality care or that an error occurred. An adverse event only indicates that an undesirable outcome resulted from a medical intervention rather than an underlying disease process [19]. As an example, if proper procedures are followed for central line placement but the patient develops a pneumothorax, this would constitute an adverse event even though all the elements of quality care were met.

Most existing typologies of definition related to patient safety pertain to medical interventions. Errors of diagnosis are emerging as relatively uninvestigated but equally important causes of unsafe patient management in the ICU [20].

MEASUREMENT OF SAFETY IN THE INTENSIVE CARE UNIT

The science of measuring and reporting patient safety remains immature and can be viewed from the perspective of whether the measure identifies a structure, process, or outcome related to safety. Different methods of measurement focus on one or more of these elements and may be more or less efficient at identifying safety risks in one or more of these domains. The primary methods of measurement include incident reporting, targeted monitoring, use of discharge data sets, process of care measurement, trigger tools, ICU audits, and direct observation [18].

Incident Reporting

In terms of collecting safety measurement data, traditional methods based on incident reporting of specific adverse events have been largely ineffective for several reasons [21]. First, reports have been generated in a punitive environment that focuses on the provider who committed an error rather than systems of care and discourages self-reporting of errors [5]. Second, each report of an error represents a "numerator" value that does not give insight into the denominator pool of patients at risk for similar errors. In the absence of these values, the incidence of errors and the overall safety of an ICU cannot be assessed. Third, definitions of errors used in incident-reporting systems vary, which impedes data synthesis, analysis, collaborative work, and evaluation of the impact of changes in health care delivery [22]. And fourth, appropriate functional data spanning the domains of structure, process, and outcome are not collected, which impedes the ability to "deconstruct" an error to understand its root causes and patient impact.

Recent advances to incident reporting have enhanced the detection and analysis of errors. Internet-based systems allow anonymous reporting of errors to encourage providers who have either committed an error or have knowledge of an error to enter related information into a central data repository. Institutional commitment to a "culture of safety" has a motivational effect on error reporting because health care providers note the impact that a reported error can generate in terms of improved quality of care. This culture requires several essential process elements to enhance error reporting: A team (a) convenes to develop preventative solutions to a reported error, (b) generates plans to improve the care, and (c) has a method for implementing and measuring the impact of their plan [23]. The Intensive Care Unit Safety Reporting System (ICUSRS) is

an anonymous reporting system that focuses on "systems factors" rather than "person factors" and provides expert analysis with feedback and guidance to improve processes of care and prevent error recurrences [11,24]. The University Health Systems Consortium's Safety Net reporting system can generate consolidated reports with application to the ICU [24].

However, problems remain with incident reporting in terms of the taxonomy used to describe errors and adverse events. The Joint Commission (JC) published a patient safety event taxonomy and classification schema for near misses, errors, and adverse events [11]. The taxonomy was designed to conform to an analytical framework and common word usages to promote its use and the understanding of its output. Data entered allows classification of a patient safety event within five complementary primary groups: *impact*—the outcome or effects of medical error and systems failure, commonly referred to as harm to the patient; *type*—the implied or visible processes that were faulty or failed; *domain*—the characteristics of the setting in which an incident occurred and the type of individuals involved; *cause*—the factors and agents that led to an incident; and *prevention and mitigation*—the measures taken or proposed to reduce incidence and effects of adverse occurrences.

The ICUSRS reporting platform similarly uses a framework for evaluating factors that contribute to an incident [11]. Both the JC and ICUSRS systems recognize that errors are multifactorial and therefore include multiple variables along the three domains of structure, process, and outcomes, such as caregiver performance, systems of care, resource availability, functioning of teams, and the environment of care. These systems describe events with a multidimensional taxonomy to allow the comprehensive description and full deconstruction of errors to determine their root causes [9]. However, even if taxonomy issues of incidence reporting are improved, the problem of determining the true incidence rate remains. A comprehensively described and deconstructed incident only gives insight into the numerator; it does not provide information on the number of patients at risk and does not allow determination of true incidence rates.

Targeted Monitoring

A complementary approach to incident reporting is targeted monitoring. ICUs can measure their patient safety outcomes by monitoring a specific indicator, such as the incidence of *Clostridium difficile* infection in the ICU or ventilator-associated pneumonia. In so doing, ICUs are challenged to define their denominators and select indicators that can be readily detected and counted to provide an accurate numerator. The denominator is especially difficult to determine because the measurement has major impact on interpretation [11]; for instance, *C. difficile* infection rates can be described per ICU patient, patient ICU days, or at-risk patient ICU days. The numerator data are equally challenging because of the time and expense of chart extraction needed for their collection. If the characteristics of the patient population change over time, then these factors must be accounted for as well. For example, if the patient population changes or new services such as transplant are offered by a given hospital, then the patient mix will change and adjusted hazard rates will be needed. Thus, for this approach to work, a multidisciplinary team that includes people with ICU training, organizational skills, database management, and epidemiology are needed.

Discharge Data

Discharge data represents a potential source of information to allow the retrospective collection of quality and safety indicators to profile ICU performance [25–27]. Recently, AHRQ has developed empiric measures of quality and safety from multistate discharge data in a redesign of the original Healthcare Cost and Utilization Project Quality Indicators [28]. The Patient Safety Indicators are relevant to ICU safety of care. Although most of these indicators relate to surgical patients, newer indicators are being designed to measure the safety of care for medical patients with critical illnesses, such as myocardial infarction, stroke, and congestive heart failure.

Although this method is powerful and can be quite useful, it is important to also recognize its limitations. Discharge data analysis gives insight into outcomes, but little information on structure or process. Large datasets such as these also have limited data quality for clinically relevant covariates, so controlling for confounders is difficult. Because all of the clinically relevant covariates are not included, the problem of residual confounding is always a problem and caution should be exercised when interpreting results. Making interinstitutional comparisons is therefore difficult, and even when trending data over time, results must be analyzed with caution. When patient populations and their problems are relatively homogenous and stable over time, this is a good system (e.g., surgical patients). When there is marked heterogeneity in terms of clinical problems and rapid changes in process of care over time, this approach will have difficulty. Having said this, discharge datasets can be an important tool for hypothesis generation so that ICU leaders can then launch more systematic studies into particular problems.

Process of Care Measurement

Safety can also be measured through determination of the proportion of patients who receive certain processes of care that have a strong evidentiary base for improving clinical outcomes. However, it may be difficult to isolate and to ascertain the contributory effect of influential factors, that is, adherence to best practice by the caregiving team, the role of complications, or level of care. Physicians and other clinicians often have a stronger sense of accountability toward a process measure than an outcome measure because the process measure can be more strongly linked to a particular care provider or team [29]. Also, physicians may believe that outcomes can be overly influenced by severity of disease and prove resistant to quality improvement efforts. To serve as an accurate measure of safety and to influence quality improvement, process measures must have a causal relationship with the outcome they are intended to represent.

Examples of process measures include approaches for ordering therapy in the ICU. Medication errors and adverse drug events occur commonly in the ICU [30] and can be limited by the use of formatted drug-ordering forms [31]. Computerized physician order entry for drugs has the potential to decrease the rate of serious medication errors [32] and to improve clinical outcomes when applied to antibiotic prescribing [33]. Additional care processes that should be in place to support patient safety can be constructed by reviewing evidence-based clinical practice guidelines [34], such as standardizing orders for ventilator management in the ICU [35].

Process of care measurement is often very effective for certain types of problems, like computerized order entry, but it is important to recognize some of the limitations and difficulties inherent in the system when applied to more complex problems. When strong evidence-based clinical practice guidelines are available, this is a feasible strategy, but often this is not the case. In addition, properly identifying those patients eligible for a particular protocol in the appropriate time period is critical. Examples include the use of thrombolytics for myocardial infarction and stroke, as well as recombinant activated protein C

for sepsis. Determining the numerator for such process of care measures is fairly easy (who actually received the drug), but determining the denominator can be more difficult and can be costly because of the time and expense needed for data collection (e.g., reviewing every chart in the emergency department of a patient presenting with angina or suspected myocardial infarction). In addition, chart abstraction in such cases usually requires a high level of expert judgment, which makes it even more difficult. Thus, process of care measurement, because of cost and time considerations, may be a suitable approach to improving safety for those problems in which there is a strong-evidence base and in which the costs of identifying the patient population (both numerator and denominator) are sustainable and warranted by the value of information obtained.

Intensive Care Unit Audits

An audit of the existing structure of an ICU can also measure patient safety. Evidence supports improved outcomes in ICUs staffed by sufficient numbers of board-certified intensivists [36,37]. Additional structure measures of safety include the presence of resources to establish ongoing competency of medical staff and residents [38], adequate nurse staffing and skill sets [39,40], and appropriate technology resources, such as smart pumps and bar coding [41]. And, most importantly, the presence of a culture of safety represents a central structure within an ICU for promoting safety. Such a culture emerges from the presence of leaders who are committed to safety and staff who understand that errors are inevitable, acknowledge that errors are to be reported, dedicate time to learn about new risks and hazards, support teamwork and open communication, and upgrade procedures and implement safeguards on a continuing basis [16]. Organizational characteristics of safe programs with low accident rates include successful safety programs with strong management commitment, safety training as part of new employee's training, frequent open contacts between workers and management, general environmental control and good housekeeping, a stable workforce, and positive reinforcement for good safety practices. Surveys exist that allow ICU directors to assess the status of their units' culture of safety [42–45]. Pronovost and Sexton [44] recommend measuring the entire hospital annually with the full Safety Attitudes Questionnaire, which has construct validity and sufficient reliability for measuring the single construct of safety culture. Once measured, the culture of safety can be improved with focused interventions for any low-scoring hospital areas, such as an ICU.

Trigger Tools

Trigger tools refer to techniques used to detect organizational signals for adverse events. For instance, orders for flumazenil may identify patients who were given an overdose of a benzodiazepine drug. The flumazenil order therefore would serve as a trigger to perform a chart review. A trigger or set of triggers can be used to identify medical records for retrospective review to assess organizational safety or used in "real time" as a tool to identify a specific patient at risk for an adverse outcome. Trigger tools for the ICU have been shown to be practical approaches to enhance detection of adverse events in critically ill patients [46].

INTENSIVE CARE UNIT ORGANIZATION

Because patient safety and quality of care are intricately related, it is vital that intensive care medicine be effective and efficient at delivering safe, high-quality care at a low cost, especially as between 0.66% and 1% of the gross domestic product in the United States is spent on critical care services [47–49]. As with any critical activity, the organization and structure of services affect its delivery [50].

The Committee on Manpower for Pulmonary and Critical Care Societies was sponsored by the American Thoracic Society, the American College of Chest Physicians, and the Society of Critical Care Medicine to make supply–demand projections about pulmonary and critical care services and physicians [51]. It was estimated that by 2020 there would be a deficit of pulmonologists equal to 35% of demand and that by 2030 the deficit would be equal to 46% of demand. The calculated shortfalls for intensivists were 22% and 35% for 2020 and 2030, respectively.

Given these shortages in physician personnel resources, it is imperative that ICUs optimize their organization and utilization of personnel. Thus, several issues regarding organization and staffing of the ICU are relevant (see Chapter 208). Current controversies in this area include whether around-the-clock intensivist staffing are required for quality care, whether closed or open ICU formats are better, and whether regional intensive care centers are necessary.

Intensivist Staffing

Twenty-four hours a day, 7 days a week (24/7) attending intensivist coverage was available in only 6% of American ICUs in a 1991 survey, and such coverage was available in 72% of European ICUs in the European Prevalence of Infection in Intensive Care survey [52,53]. Given the discordance in around-the-clock coverage across the Atlantic Ocean, there is surprisingly little evidence to support the benefit of 24/7 coverage of ICUs by senior intensivists. In fact, many academic institutions in the United States offer 24/7 coverage by dedicated house staff and other physician extenders with critical care attending backup, either by pager or mobile phone, without any temporal changes in mortality or utilization of resources [54].

There has been much speculation regarding the benefits of continuous, on-site attending physician coverage in the ICU [55–58]. Hypothesized benefits might include decreased mortality, decreased length of stay, decreased global costs (although ICU costs might be higher), decreased complications, improved nutritional management, efficient admission and discharge policies, improved reimbursement, and improved ICU team functioning. Within the context of patient safety, improved staffing ratios would presumably tend to reduce latent errors and mistakes. A single, retrospective pre- and postintervention study examining 24/7 intensivist coverage in the United Kingdom did show a decline in mortality with institution of continuous, on-site attending coverage [59]. Others studies have continued to support the benefits of intensivist involvement in critical care, even in ICUs where control was maintained by primary care physicians. Intensivist involvement also has been demonstrated to improve outcome in settings involving surgery of the abdominal aortic and esophagus, pediatric critical care and combat injuries. On balance, however, there are little data supporting the hypothesis that attending intensivists need to be on-site on a continuous basis to provide cost-effective quality care. In fact, a multicenter retrospective analysis suggested that there was a higher mortality rate when critically ill patients were managed by intensivists [60]. Although issues of confounding and controlling for these factors are always at issue in retrospective analysis, this study (Project Impact) has only reinforced the need to further study optimal staffing and training for critical care personnel.

Higher staffing ratios, whether nursing or physician, should theoretically eventually improve quality of care; for example, 1:1 patient-to-nurse ratios and continuously available on-site physicians from all specialties. The real issue centers around the

incremental costs and benefits of improved staffing ratios compared with the current ratios (generally, 2:1 patients-to-nurse and variable attending coverage). We can restate the question as, given the finite and constrained resources we have, what is the optimal physician staffing ratio and organization for ICUs from a societal cost-effectiveness perspective? Currently, there are insufficient data to answer this question and indeed the "correct" answer is probably contingent on many other factors, including societal values, economic resources, physician manpower considerations, nursing costs and availability, nurse training, availability of house staff, house staff training, organizational culture, technology costs, and legal considerations.

As an example, if resident and fellow house staff are available, ICU nurses have advanced training and good organization, the number of patients in the ICU is small, and the clinical population has relatively straightforward problems, then in-house, 24/7 intensivist coverage is less likely to be cost-effective compared to intensivist backup (on-call). However, if ICU size goes up, complexity of patient problems increase, house staff training for ICU-related problems goes down, and there is a high amount of nursing staff turnover, which limits their expertise, then 24/7 intensivist coverage may have more benefits. The interaction of many of these variables makes study of this field complex because multiple variables have an impact on each other as well as an impact on safety and outcomes, but the issues of patient safety and the potentially high costs of instituting 24/7 coverage warrant further prospective studies.

ICU Models

The 24/7 intensivist staffing variable is a critical element of several variables determining ICU safety as it impacts errors of omission and recognition and can reduce critical mistakes. However, in addition to the actual number and availability of intensivists, how they are organized is equally and possibly even more important if cost-effective quality care is to be delivered.

One aspect of organization that can impact care is whether an ICU uses an open or closed model. Much evidence suggests that in an open ICU, intensivist consultation should be required for critically ill patients [61]. More ideally, however, critical care services should be delivered in closed units with dedicated intensivist staffing with administrative structures that allow for rapid implementation of protocols that have been proven to be beneficial to patients [54,62,63]. It might even be possible that a closed ICU functions efficiently without implementation of protocols as suggested by a nonblinded study [64,65]. Closed units also allow for strong leadership coupled with a multidisciplinary team approach to patient care, which might allow for effective and efficient delivery of services in the manner envisioned by the Society for Critical Care Medicine [50,66,67].

From a patient safety perspective, strong evidence-based protocols offer many potential advantages. They can help to minimize both slips and mistakes. For instance, daily assessment of patients to determine if they should undergo weaning from mechanical ventilation is important, but in the busy ICU environment, this can easily be overlooked. The liberation of patients from mechanical ventilation via protocols has been studied by Ely et al. (1996 and 1999) [63,68]. In a randomized, controlled trial of 300 intubated adult patients, Ely et al. [68] showed that early identification of patients capable of spontaneous breathing via daily screening by other physicians, respiratory therapists, and nurses could decrease the duration of mechanical ventilation by 1.5 days when compared to patients in whom their attending physicians made decisions about extubation on an individual basis, despite the fact that the intervention (e.g., daily screening) group was more ill. In a subsequent study, Ely et al. [63] showed a respiratory therapist-directed weaning protocol *without direct physician supervision* could be instituted in the ICUs of their university medical center with modest degrees of success. This would constitute one example in which protocols, disseminated through a closed ICU organization, can improve safety by limiting slips.

Other management strategies, such as sedation and ventilator management of ARDS/ALI are well suited for development of protocols and may further limit mistakes, such as over- or undersedation in the ICU [69,70] and enhance use of lower tidal volume ventilation. Nurse-driven protocols with specific sedation targets and daily lightening of sedation have been shown to impact duration of mechanical ventilation.

Intuitively, it seems that protocols would be easier to institute using a closed ICU organizational structure rather than an open structure. Protocol development, dissemination, and implementation are all facilitated by having a stable, smaller number of physician providers rather than having many providers with varying practice patterns. In addition, development and implementation of protocols allows for process of care measures to be built into the system, so that the measurement of safety in the ICU can be achieved in a more cost-effective manner.

Regional Intensive Care Unit Centers and Telemedicine

The Leapfrog group (http://www.leapfroggroup.org) is a consortium "made up of more than 170 companies and organizations that buy health care." The consortium's overarching objectives are to improve the quality, safety, and affordability of health care, including the way critical care medicine is practiced. What distinguishes Leapfrog from other quality-improvement organizations is its tremendous economic clout. Their current recommendations for ICU organization are that (a) ICUs should be managed or co-managed by intensivists who are dedicated to the unit and who are physically present during daytime hours, and that at other times, (b) the intensivists can return pages within 5 minutes, and (c) that the intensivists can either reach the ICU or can arrange for physician extenders to be on-site within 5 minutes. Whether or not one agrees with these recommendations (often misinterpreted as requiring on-site 24/7 intensivist coverage), many hospitals are attempting to adhere to the standards set forth by the Leapfrog group. Their recommendations for ICU staffing and practice are primarily based on "common sense and rational extrapolation of the data"[71]. Because *there are not* and will not be enough pulmonologists and intensivists to staff all hospitals in the fashion suggested by the Leapfrog group [51], there will need to be alternative acceptable schemes for the delivery of critical care services.

One potential solution is the regionalization of intensive care services in a hub-and-spoke pattern similar to airports [67,72]. In 1994, the American College of Critical Care Medicine challenged the medical community to study the regionalization of ICUs [36]. Since then, however, only a few studies have directly examined the issue of transferring adult critically ill patients from community hospitals to larger tertiary care centers [73,74]. In a retrospective, case-controlled study, Rogers et al. [73] showed that trauma patients could be safely stabilized at smaller, outlying community hospitals prior to transfer to a level I trauma center. Similarly, Surgenor et al. [74] showed in a prospective fashion that interhospital transfers of patients requiring high-level critical care were as safe as intrahospital transfers. Both of these studies hint at the feasibility of safely regionalizing critical care services as one method for partially dealing with the likely shortage of physicians trained and dedicated to critical care medicine [51]. In addition, higher volume centers have been demonstrated to have improved outcomes in patients with sepsis and respiratory failure requiring mechanical ventilation, thereby reinforcing the case for transfer to regional centers of critical care excellence.

However, even if transfers can be accomplished safely, it is not clear that regionalization can deal with the significant shortages projected. Regionalization of high-level services may allow some economies of scale to be recognized, but it is unlikely that these benefits could fully offset the shortages projected.

Another increasingly used model involves telemedicine [75]. In this paradigm, one or several ICUs are electronically linked to a central and remote site where intensivists monitor critically ill patients. For instance, ICUs (patient rooms and nursing stations) can be linked to the remote site via cameras, speakers, and microphones. The hospital computer and data system, order-entry system, ICU and telemetry monitors, digital radiography, and any other required information systems can be linked remotely to intensivists. This allows for oversight of ICU activities without actually requiring that critical care physicians be physically on-site. Procedures can then be performed by on-site physician extenders while the ICU nurses can carry out orders. The patients' primary physicians or daytime intensivists can then choose to be involved to varying degrees during off-hours.

Two studies have been published examining the feasibility of ICU telemedicine and the associated patient outcomes [76,77]. Rosenfeld et al. [77], compared a single prospective intervention arm to two retrospective baseline arms (one arm to exclude seasonal variations and the second to account for temporal changes in outcome) of surgical ICU patients, and found that severity-adjusted ICU mortality, severity-adjusted hospital mortality, ICU length of stay, and complication rates all decreased by a statistically significant amount while concurrently lowering costs. Breslow et al. [76] demonstrated similar benefits when linking multiple ICUs to a remote monitoring site using commercially available equipment. Nonetheless, another study of the effectiveness of telemedicine failed to conclusively demonstrate improved outcomes or length of stay [78].

In a previously well staffed critical care system, the addition of an supplementary layer of telemedicine monitoring improved hospital and ICU mortality and length of stay. Adherence to critical care "best practices" was also improved [79].

PHYSICIAN TRAINING AND DEVELOPMENT OF A CULTURE OF SAFETY

It is during residency training that physicians acquire not only their clinical knowledge, but also their familiarity with system-based practice attitudes toward patient safety. Because development of a culture of safety is one of the key elements to solving patient safety issues, the training of residents is central to developing long-term solutions to patient-safety problems. However, the ICU experience can be one in which residents themselves become a safety issue. Residents need to acquire the body of knowledge, skills, and experience necessary to function as attending physicians, and as part of this training they need to develop a culture of safety. Yet, lack of supervision, experience, and resident fatigue can adversely affect patient safety, especially in the ICU setting. It is thus useful to separate the issues of safety into those related to proper resident training, which affects the culture of safety in the long term, and those related to resident performance, which impacts patient safety in the short term.

Teaching a Culture of Safety

Poor outcomes related to resident errors have been documented by up to 45% of house officers queried, with nearly one third of the incidents associated with patients' death [80]. Resident cross-coverage and hand-offs also increases the risk of medical errors. The harried work environment and heavy workloads add to the risk of medical mishaps. It is within this context that residents are also acquiring their attitudes and the habits that determine their culture of patient safety. There is typically limited integration of safety practice into work routines [81]. To address these issues, governmental, local, and educational organizations have focused on how patient safety can be integrated into the continuum of medical education. Only a small proportion of clerkships and directors of clerkships, in the medical student setting, have patients' safety content as part of course curricula. Limited exposure of medical students to quality management, quality improvement, and organizational problem solving, has prompted curriculum guidelines that require residents to develop competency in six areas, including; patient care, medical knowledge, patient-based learning, personal and group communication skills, professionalism, and system-based practice [81,82]. Patient-based learning and system-based practice are the areas most relevant to patient safety and the development of a culture of safety.

The traditional morbidity and mortality conference in medical school-teaching hospitals has been an important training forum, for discussion of adverse events and errors as well as inculcating a safety culture. Data show that Internal medicine conferences were longer than surgery conferences and allowed more time for listening to invited speakers but had less time in audience discussion. Problematic cases in medicine were less often attributed to root causes. There was less frequent acknowledgement of specific errors in the medical cases compared with those in surgery [83].

Resident and Trainee Performance

Optimal resident and trainee performance requires adequate rest, supervision, and sufficient training to perform increasingly complex problem-solving tasks. Each of these areas can contribute to safety as they represent potentially latent medical errors (errors due to the design of the educational system as well as the health care delivery system).

Preparing for work by getting sufficient sleep and enhancing alertness is a recognized responsibility of the clinician. Despite this seemingly obvious axiom, extended work hours and extreme fatigue among trainees are long-standing traditions in medical education and have often been the hallmarks of "excellence" in educational programs. Prolonged work hours and being on call was exceedingly common, with workweeks of 120 hours and on-call shifts of 48 hours not unusual. However, resulting fatigue has been associated with altered moods, depression, anxiety, confusion, and anger, and, most recently, impairment in clinical performance [84,85]. Among documented impairments were decreased technical dexterity, impaired clinical reasoning, and inability to learn and accommodate new information. In a recent study of medical house staff in which work was limited to 16 and fewer consecutive hours, trainees slept more and had less than half the rate of attention failures compared to traditional "long" schedules. Interns working extended shifts of 24 to 30 hours had greater attention failures and performance associated with significantly more medical errors compared to those scheduled to work only 16 consecutive hours [86,87]. These findings have been observed across medical specialties with prolonged shifts associated with decreased attention, vigilance, and simulated driving performance similar to blood alcohol level of up to 0.05%. In addition, the odds of having a motor vehicle crash were significantly increased after prolonged work shifts. Extended shifts increased the amount of risk of any motor vehicle crash and falling asleep at the wheel [88]. Although preliminary studies have demonstrated significant improvement in mortality in common hospital

diagnoses (acute myocardial infarction, congestive heart failure and gastrointestinal bleeding) in the first 2 years following these reform measures, cost estimates for these reforms have been estimated at $1.7 billion [89,90].

An assumption that improved work schedules will lead to improved patient outcomes has led to significant regulatory intervention to limit trainee work schedules. Following the 1984 Libby Zion case, New York State, adopted regulations that limit resident work hours to 80 hours per week, and with increased supervision [91]. The Accreditation Council for Graduate Medical Education (ACGME) has set standards for work hours and time off, although these vary among the specialties. The Association of American Medical Colleges issued duty hour regulations in July 2003. The purpose of these rules was to limit the number of weekly work hours, continuous hours, call frequency and set a minimum time between on call and insuring days off in between [92]. Direct federal regulation of work hours and duty periods for house staff has been introduced to the United States Congress [88], but federal policy also requires ACGME certification. In addition to regulating trainees, other proposed JC standards for 2008 may include recommendations to set limits on physician and nurse work schedules to reduce fatigue and thereby the frequency of medical errors.

Even when trainees have sufficient rest, they still require adequate training and supervision. The question becomes how to acquire sufficient experience while minimizing patient risks. Previous paradigms of critical care education have emphasized knowledge acquisition over performance. The critical care unit poses unique educational obstacles. Limitations of current training practices include difficulty in procuring cadavers, and tissues. There are ethical and financial barriers to utilization of animals. "Real" patients are increasingly reluctant to be used as a training tool. Critical care procedures are often dangerous and extremely difficult to learn and teach. Because of the learning curve, patients may be harmed, and the phrase "see one, do one, teach one" may no longer be relevant to modern practice.

One option that is being increasingly used in the ICU is simulation. Simulation is the imitation or representation of a potential situation in an experimental setting. It can be used to train physicians in the cognitive, procedural, and problem-solving aspects of critical care. Simulation has been increasingly used as an effective tool for training in medical settings [85]. First pioneered by Edward Leap, who designed a flight simulator for pilots in the 1920s, simulators are used today by all commercial airlines, by astronauts, the military, and the nuclear power industry. Medical simulators today frequently incorporate computers and virtual reality, but it is important to recognize that simulation training does not necessarily imply use of a computer. Simulators have traditionally focused on cardiopulmonary resuscitation models and normal/abnormal heart sounds, but many forms of simulation training are becoming available. Other simulators relevant to the ICU include mechanical models of the airway to teach basic bronchoscopy as well as newer bronchoscopy simulators with virtual reality augmentation [93]. The type of simulator (computer driven, mechanical, or a combination) depends upon the task being learned. For critical care, tasks can be broadly grouped into cognitive tasks (e.g., knowledge of physiologic responses to ventilator changes, analysis of cardiac rhythms in ACLS), mechanical-procedural tasks (e.g., bag-valve mask ventilation [94], intubation [95,96], bronchoscopy [93], central line placement [97]), and team performance tasks (e.g., respiratory failure using the Anesthesia Crisis Resource Management (ACRM) course [98], ACLS [99]). Simulation has been applied to all three areas. The incremental benefit of simulation training as compared with standard teaching methods on real-life performance has been demonstrated in only a few studies [93,97,100]. However, there is a much larger body of evidence in which surrogate outcomes (not real-life performance per se) have been used to demonstrate the positive effects of simulation training. Surrogate outcomes in these cases have included measures of student confidence [97] or performance on a model [94–96,99]. On balance, while the current evidence base is still incomplete with only a few randomized trials documenting superior real-life performance after simulation training, it reasonable to conclude that simulation training will play an increasingly important role in critical care education. The advantages hypothesized for simulation include safety, efficiency, and availability. Intricate elements of difficult procedures and potential complications as well as the response to equipment malfunction can be selectively and repeatedly rehearsed. The ability to provide immediate feedback and train teams is also enhanced. Employing simulation models may positively impact direct and indirect costs associated with training and educating personnel through reduced use of operating rooms and may potentially reduce malpractice claims. It is anticipated that as the expense of such equipment diminishes, simulators will be increasingly adopted in medical school curriculums and residency training.

The Agency for Health Care Quality and Research has made development of simulation devices and protocols an important priority. At the present time, there is only limited clinical evidence supporting the efficacy of simulators on improving patient-based outcomes such as length of stay and mortality.

REGULATION AND GOVERNMENT IMPACT ON PATIENT SAFETY

The role of government and nongovernmental regulation has increased during the past decade and taken on an international scope. As the public has become more aware of the need for patient safety and quality improvement within health care, there have been many new regulatory and reimbursement initiatives originating from the public sector (federal and state governments and agencies [e.g., www.ahrq.com]), state and county health departments, purchasers, and nongovernmental organizations (e.g., JC, ACGME), and international organizations (e.g., World Health Organization [WHO]). The hypothesis that significant mortality can be attributed to medical error has facilitated the implementation of rules and guidelines. Regulatory efforts encompass rules and regulations but also accreditation of organizations, certification of providers, and reimbursement programs based on patient safety processes and outcomes. Purchasers, led by the Centers for Medicare and Medicaid Services have adopted pay-for-performance reimbursement models [101] and nonreimbursement strategies for complications of care-related to specific "never events" [102]. A new area of interest pertains to appropriate levels of regulatory oversight for patient safety research that ensures patient protection yet fosters the acquisition of new knowledge necessary to improve patient care in the ICU [103].

Many regulatory initiatives are likely to improve outcomes, but others overlap thereby presenting a risk for causing confusion and malaise in health care providers as they attempt to comply with conflicting rules, mandates, and guidelines, and may actually become impediments to patient safety. Two trends include greater collaboration in developing safety efforts between relevant organizations and emergence of international partnerships of regulatory organizations. These efforts may result in improved harmonization of standards and regulations.

In regard to physician-related accreditation and certification, the ACGME has included patient safety concerns in its resident program accreditation process both in mandating duty hour limitations and requiring the inclusion of patient safety in educational curricula. The American Board of Medical

Specialties requires evidence of practice improvement efforts for maintenance of certification. Some of the required modules include patient safety domains. Regarding organizational-level regulations, the JC publishes annually an update of its national patient safety goals in support of their standards for accreditation, which include ICU-related processes of care [104]. In 2005, the JC and Joint Commission International were designated by the World Health Organization (WHO) as the first members of the WHO Collaborating Centre for Patient Safety Solutions. The Collaborating Centre has organized an international network to identify, evaluate, adapt, and disseminate patient safety solutions (http://www.ccforpatientsafety.org/WHO-Collaborating-Centre-for-Patient-Safety-Solutions-continued/). This effort demonstrates the international intent to create linkages with key organizations and individuals with expertise in patient safety, which include accrediting bodies, national patient safety agencies, professional societies, and others.

Independent, not-for-profit organizations, such as the Institute for Healthcare Improvement (IHI), develop programs to accelerate improvement by promoting cultures for change, stimulating promising concepts for improving quality and safety, and assisting health care organizations to implement these new concepts. The IHI has had considerable influence on regulatory organizations with respect to adoption of IHI initiatives, such as ventilator bundles, central line bundles, sepsis bundles, intensivist staffing models, and rapid response teams (http://www.ihi.org/IHI/Topics/CriticalCare/IntensiveCare/Changes/IntensiveCareChangesIndex.htm). Because of the emphasis on rapid promotion of promising new interventions, such organizations have occasionally endorsed interventions prematurely, such as tight glycemic control, ahead of supporting evidence.

Other proposed areas of regulation include minimum nursing staffing ratios to meet workload demands [105] for Medicare-participating hospitals and limitations of excessive work hours for nurses and residents. Hospitals have also been required to implement specific improvements and to develop a program for quality assessment. The IHI has also suggested that a patient safety officer needs to be an important component of all large health care organizations [106].

Safety has become a major concern in the high-risk environment of the ICU. Integrated and coordinated systems that identify patient safety problems and report them back to providers so they can improve their performance and so that they can improve "their structure, processes and outcomes of care" are being implemented. ICU reporting systems identify trends and patterns that facilitate health care improvement and reduction of preventable medical incidents. Because safety and error prevention in the health care setting compares unfavorably with those of other industries, a major thrust has been to adopt strategies and technologies that have proved successful in other settings and to apply them to the ICU. Common definitions of health care-related safety concepts and systems for safety monitoring and reporting will improve individual and group capability to improve patient safety. Approaches that have been implemented to some extent in the ICU community include incident reporting, targeted monitoring of process of care and discharges, trigger tools and ICU audits. Integration of electronic ICU patient data, such as hospital admissions information, laboratory results, progress notes, imaging and authentication data, with non-ICU patient data across a hospital computerized medical record is a prerequisite for promoting patient safety. ICU organization and staffing models also impact safety in the ICU and continue to be studied [107] along with team-training efforts [108] and programs in critical care telemedicine. Hospital design with placement of the ICU adjacent to emergency departments and surgical suites to facilitate rapid transfer of unstable patients will come under increased review. Although regulation by public sector agencies will impact the safety of the critical care environment, developing a culture of safety through graduate and postgraduate medical education will also be a major part of an ongoing program of quality improvement.

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CHAPTER 211 ■ MEDICAL ETHICS, END OF LIFE CARE, AND CLINICAL RESEARCH IN THE INTENSIVE CARE UNIT

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Scientific knowledge and technology dominate the intensive care unit (ICU) environment and the practice of critical care medicine. Caring for the critically ill person challenges our ability to apply knowledge in the best interest of the individual. The critical care physician is confronted by complex medical decisions, life-and-death circumstances, and a person who is frequently unable to communicate. This makes it difficult to intimately understand their moral values and wishes at the time when these values are most meaningful. Moral issues are inescapable in the course of critical care and occur so frequently that resolving some issues becomes a matter of routine. Deciding what we should do for the welfare of our patients is guided not only by scientific knowledge, but also by understanding numerous other complex and evolving attributes of the physician–patient relationship including: moral responsibilities to patients, legal obligations, and the role of the patient in decision making. This chapter provides an overview of current practice of guiding patients or families in making decisions about critical care, withdrawing life-sustaining treatments, and participating in clinical research.

Moral obligations of physicians to their patients have been recognized for millennia, and are described in the Hippocratic Oath (400 BC), the Oath and Prayer of Maimonides (1783), Nuremberg code (1947), The Belmont Report for protection of human subjects in research (1979), and contemporary guidelines and codes for physicians [1–3]. Whereas ancient and traditional descriptions of physician responsibilities emphasized trust, compassion, fairness, caring, and acting in the best interest of patients, contemporary conceptions of the patient-physician relationship emphasize the patient's individualism, or autonomy in decision making. This change in emphasis appears to have evolved along with social, political, and judicial prominence of respect for individuals along with a growing social mistrust of commercialized medical care and clinical research during the past 40 years. Humane care based on a foundation of trust remains the responsibility of the physician, particularly in the ICU where patients may have lost their ability to advocate and to be self-governing due to their illness, fear of dying, and limited understanding the scientific basis of their treatment.

Ethics is a branch of philosophy that concerns the analysis of moral obligations, values, and choices. Ethics involves deliberation and reasoning about the best course of action and results in a clearly delineated path to a decision. Critical care physicians apply ethical reasoning to make moral decisions with patients in the ICU. The ethical questions that confront physicians are practical, not theoretical, and the answers lead to decisions about the best choices in the care of patients.

PRINCIPLES OF BIOETHICS

Medical ethics is a one branch of bioethics. The ethical framework generally used for medical decision making is reasoning from ethical principles [4–6] (Table 211.1). The oldest principles are *beneficence* and *nonmaleficence*, and other principles have been described in recent decades. *Justice*, or fairness, implies that patients will be given the treatment that is indicated for their condition without regard to social, economic, ethnic, or other attributes. Unfortunately, there may be times when resources such as ICU beds or mechanical ventilators are limited and ICU physicians may need to work with hospital administration and the community to clarify how care may be rationed [7]. At the time this chapter was written, a global influenza pandemic was predicted [8,9]. *Patient autonomy* has, in recent years, become foremost among ethical principles. This emphasis on the importance of individual choice has been

TABLE 211.1

PRINCIPLES OF BIOETHICS

Beneficence: physicians act in the best interests of the patient
Nonmaleficence: physicians exercise caution when providing treatment
Justice: physicians allocate resources fairly
Autonomy: physician and patient deliberate about patient goals when deciding on medical therapy or research participation

influenced by numerous social changes and increasing distrust of the corporations and medical centers. Several highly publicized instances of inappropriate medical research in the United States during 1960 to 1980 led to legislation and policies defining the place of informed consent in research and in medical care. Autonomy is the foundation for the practice of informed consent for medical research and clinical care. Autonomy is exercised by patients but must be enabled by physicians and is based on an assumption that the competent informed person can weigh risks and benefits and make a decision that balances their medical needs and personal values. Autonomy requires that the patient or surrogate is able to deliberate about personal goals and act under their own direction (self-governance). The joint participation of physician and patient in "shared decision making" is recommended [10,11]. Unfortunately, it is usually not possible for ICU patients to share decision making due to the nature of their illness and life support devices. The physician plays a role by acknowledging the importance of autonomy and ensuring that a surrogate is identified as a decision maker.

Acknowledging the importance of autonomy emphasizes the role of the individual patient in decision making. To make decisions, the patient or surrogate must have information about the possible risks and benefits of an intervention. The ICU physician must provide information about the diagnosis and prognosis of the critical illness that will be used in a decision of consent or refusal. The competent and informed patient has the ability to consent to, or refuse, medical interventions or research. Because autonomy means that a person has ability to make decisions on all aspects of their life, the autonomous person may choose to not only oppose the advice of physicians, family, and friends, but may also choose to act contrary to their own previously expressed wishes and can change their mind. If a person lacks autonomy then their ability to speak for themselves can be protected by referring to a substitute such as previously expressed wishes or a surrogate decision maker.

Patient autonomy alone is not sufficient to describe the patient–physician relationship and the physician remains obligated to their own moral responsibilities and to acknowledging the values of the patient. In practice, the principles already described represent different values that must be considered and balanced against each other when reasoning toward a treatment decision by asking the question: how much potential benefit at how much risk is acceptable to this critically ill person? Beyond these generally accepted principles there are many other perspectives that may influence decision making, such as religious authority, the importance of relationships, the rights of the patient, or the value of patient care to society. It is possible that patients, families, or ICU staff will appeal to other ethical perspectives when reasoning toward a treatment decision, and while the patient is free to reason from their own ethical value system to guide their choices, the four principles are the standard guiding principles for the ICU physician.

DETERMINING DECISION-MAKING CAPACITY

To exercise autonomy, a patient must have the capacity to make a choice. Determining whether a patient has capacity occurs daily in the ICU and the critical care physician should be adept at this assessment. Physicians use criteria listed in Table 211.2 [12,13] and also must comply with local hospital policy and state law when determining decision-making capacity. Decision making capacity is decision specific; that is, patients may have the capacity to make some decisions but not other decisions. Capacity is determined one decision at a time by a physician (in contrast to competency that is determined by the courts).

All of the criteria listed in Table 211.2 must be present, or the patient lacks capacity. When the critically ill person is unable to make decisions, the physician must document lack of capacity and plans for making decisions. Historically, physicians and/or a capable family member made decisions. Currently, patients are likely to use advance directives or assign surrogate decision makers to make medical decisions should they become incapacitated. Patients with terminal disease can address situations where death is imminent and there is no hope of recovery by preparing advanced directives, or living wills. Advance directives are also useful for patients who indicate that they would refuse life support under any circumstance. However, in many cases, the circumstances of a patient's critical illness may be unanticipated, prognosis may be unknown, and written directives may be ambiguous. In the absence of a clear advanced directive, surrogate decision makers provide a "substituted judgment" for the incapacitated patient based on their knowledge of the patient's values and previous statements made by the patient. Surrogates are most often relatives of the patient either through legal authorization by the patient prior to their illness, or as permitted by state laws. To fulfill the role, a surrogate must disregard their own values and represent the values of the patient. An incapacitated patient can accept or refuse therapy through a surrogate. Refusal of therapy has been legally guaranteed to patients for decades, and the results of landmark cases of permanently incapacitated patients in persistent vegetative states refusing therapy through surrogates can be extended to ICU patients. Cases such as *Quinlan* (1976), *Cruzan* v. *Missouri* (1990), and *Schiavo* (2003–2005) led to laws that permit refusal of therapy through a surrogate. In many states, surrogates are required to now bring forward "clear and convincing evidence" in verbal statements from the patient prior to incapacitation to justify refusal of therapy [14–17].

PHYSICIAN RESPONSIBILITY FOR THE INCAPACITATED PATIENT

Physicians identify lack of capacity and confirm the need for a surrogate decision maker. Physicians may have discussed with the patient their understanding of, and wishes for, life support prior to critical illness. But, although obligated to act in the best

TABLE 211.2

CRITERIA FOR DECISION-MAKING CAPACITY

1. The patient communicates a choice
2. The patient understands the relevant information
3. The patient understands the situation and consequences
4. The patient manipulates the information rationally

interest of patients, there is a limit to the authority of physicians and they cannot make value decisions without taking into account the wishes of the patient. Physicians may have limited information about the values of a patient, they may have a very different set of personal values, or may have financial conflicts of interest with patient wishes [4]. Physicians cannot function as a patient surrogate to make decisions, but, in the capacity as treating physician, can refuse to perform procedures or provide care that they believe are unnecessary or non-beneficial [18–21]. Usually patients or surrogates can be dissuaded from unnecessary care by engaging in a thorough discussion of the appropriate care, reasons for refusing care, and offering a second opinion. Physicians are not compelled to perform services that violate their own moral values and can arrange for another physician to care for the patient. When patient wishes are known or communicated through a surrogate, the physician should attempt to carry these out, and obtain consent for procedures. Although some procedures can be justified without consent in the absence of previously expressed wishes on an emergency and life-saving basis, unless there is a justification physicians risk the charges of battery or negligence if procedures or other interventions are provided without consent or after refusal of consent [5,22,23].

Remarkably, surveys of ICU physicians have found that decision making practice varies greatly and often does not involve the patient. Some physicians report that they continue life support even when there is little hope of benefit from intensive care. The results of the SUPPORT study indicated that physicians did not consistently document or write a DNR order for patients that did not wish to have cardiopulmonary resuscitation (CPR) [24]. A survey in 1999 of ICU physicians from 16 European countries indicated that 73% of ICU's frequently admitted patients with no hope of survival. DNR orders were followed only 58% of the time. Yet, on the other hand, many physicians withheld therapy for patients who had no prospect of meaningful life, or deliberately administered large doses of drugs until death ensued. Only 41% of physicians surveyed felt ethical issues should involve patient and/or family [25].

Many patients with terminal illnesses will come to the ICU for resuscitation or monitoring prior to their deaths. CPR has little likelihood of improving survival of patients with terminal illnesses, and is usually regarded as nonbeneficial. Such a procedure with a low likelihood of success can be regarded as not in the best interest of the patient. This differs from medical futility, since futile care is defined as having no physiological rationale or care to which the patient has already failed to respond [4,18]. The term "futile" carries an important meaning and should be used carefully and accurately. When death is imminent and treatment has failed, then withholding futile care is supported by legal precedent. However, when death is not imminent, physicians may not be able to predict outcome. In one study, daily surveys of ICU staff found that physicians and nurses were unable to predict survival and quality of life 6 months after ICU. Nurses were incorrect in 58% of 45 patients and physicians were incorrect in 27% of 26 patients. Only one of the survivors about whom physicians believed care was futile reported poor quality of life 6 months after ICU [26]. A larger study that investigated determinants of withdrawal of mechanical ventilation found that physician's prediction of low likelihood of survival (< 10%) was a factor associated with withdrawal of mechanical ventilation and/or death [27]. In this study 3.6% of patients survived to hospital discharge after withdrawal of mechanical ventilation. A decision to withdraw support in this study was associated significantly with physician's perception of the patient's preferences about the use of life support. The ICU physician needs to know the precise hospital and legal definitions for "futility" and avoid invoking the term in cases where care is perceived as carrying a low likelihood of success or sustaining an unacceptable quality of life that is better termed nonbeneficial. If there is a plan to withhold support or procedures, for example, CPR, and the procedure is not strictly futile, then information should be provided about the procedure and rationale should be explained to the patient/surrogate [20,21,28].

ETHICS COMMITTEES

Ethics committees or ethics consultants provide an additional resource for resolving ethical conflicts. The committee is an objective "third party" not previously involved in disputes of the case. Committees review the medical and ethical and psychosocial aspects of the case and provide an ethical analysis. Committees can also provide social and emotional support to families and may be able to discuss and explain the ethical issues for longer periods of time than physicians and nurses. Since most ethics consultants are employed by the hospital, families may perceive a bias in favor of physicians or an attempt to protect the interests of the hospital. However, ethics consultants are usually well received by both physicians and patients/surrogates [28,29]. In addition to resolving conflicts, ethics consultations are associated with decrease in the duration of ICU length of stay and use of life-prolonging treatments for patients who ultimately do not survive [29].

COMMUNICATION WITH PATIENTS AND SURROGATES

Numerous studies and ICU practice guidelines over the past decade emphasize the importance of effective communication with, and support of, families of critically ill patients. Communication about plans for patient care most often takes place between physicians and family members, rather than between physicians and patients [30]. Discussions with families frequently occur when physicians have decided that continuation of care will be ineffective, but interviews with families indicate that more than half of family and patient representatives do not fully understand the prognosis and treatment plan [31]. To facilitate shared decision making, in which physician and family jointly reach a decision, communication must be more effective and needs to begin early during the ICU stay [10,11].

Physicians are more likely to achieve effective communication when meetings begin earlier in the course of care. In one study, proactive, formal, multidisciplinary meetings were held within 72 hours of ICU admission for patients with clinical features including a predicted ICU stay longer than 5 days, or predicted mortality greater than 25%. In these meetings the medical facts, the patient's perspectives on death dying and critical care, the care plan and the criteria for determining success of the care plan, were discussed. Intensive communication decreased ICU length of stay and allowed earlier access to palliative care [32]. Consistent proactive communication with families for updates on progress and encouragement to use advanced support when appropriate is recommended [10,11]. Improved communication can also be facilitated by using a private place for discussion, listening, empathic statements, acknowledging family emotions, focus on patient values and treatment wishes, clear explanation of the principle of surrogate decision making, assurance that the patient will not suffer, and support for the decisions made by the family [32–37]. A simplified mnemonic for important elements of effective physician–family communication is VALUE (Value and appreciate what is said by family members, Acknowledge the family members' emotions, Listen, Understand who the patient is as a person, Elicit questions from the family members) [39].

Families of ICU patients suffer and may develop long-term mental health issues related to the trauma of witnessing the ICU treatment or end-of-life care of a loved one. Symptoms can include posttraumatic stress disorder (PTSD), anxiety, and depression [33,40]. It is now clear that physicians have an opportunity to lessen the suffering of the family members through effective communication with families about prognosis and care of ICU patients. In one multicenter trial [38], proactive end-of-life conferences with relatives of patients dying in French ICUs resulted in better long-term psychological outcomes in the family members when compared with customary end-of-life conferences. The proactive communication intervention followed detailed guidelines [41], physicians focused on achieving the elements of effective communication summarized by the mnemonic VALUE, and family members received a brochure on bereavement. Physician–family conferences were longer (median 30 minutes vs. 20 minutes) and relatives spent more time talking (median 14 minutes vs. 5 minutes) in the intervention group. Relatives that participated in the proactive intervention had lower prevalence of PTSD symptoms, depression, and anxiety when interviewed 90 days later [38].

Ethical reasoning is part of shared decision making about ICU care for individual patients usually conducted together with a patient surrogate. Family conferences are important for facilitating care of the incapacitated ICU patient and are a forum for providing accurate prognostic information; whether the prognosis is that the patient is expected to survive or, at the other extreme, unlikely to benefit from critical care [32,42]. When a decision is made to forgo life-sustaining treatments and change to end-of-life care, effective communication serves the best interests of the patient and can improve the psychological well being of the surviving relatives.

Discussions that prepare families for the death of a patient or to discuss withdrawal of life support are an increasingly important part of a critical care physician's practice [30,43–45]. Interviews with surrogate decision makers suggest that accurate and timely prognostic information is preferred [46]. There was, however, no clear preference among surrogates (with surrogates divided for and against) about whether it was appropriate for physicians to make a recommendation about withdrawing life support [47]. Surrogate perceptions of communication and end-of-life care can be improved [48,49] and quality improvement can be assessed by means of several survey tools or outcome measures [50–52].

Among the ethical principles described in the preceding section, autonomy is emphasized in the United States. In contrast, this may not always be the case in European countries, where regional and national practices regarding the role of families in decision making, and legal and medical opinions about withholding or withdrawing life support, vary widely [25,53–57].

END-OF-LIFE CARE IN THE INTENSIVE CARE UNIT

Death remains a common occurrence in ICUs, with an estimate suggesting that as many as one in five Americans die during an episode of care that included an ICU admission [58]. Data from North America as well as Europe suggest that the percentage of patients dying following a decision to withdraw or withhold life-sustaining treatments is substantial, and increasing. Thus, critical care clinicians are effectively "managing" the process of death and dying in ICUs with increasing frequency [43,53,59–61]. A number of problems and challenges have been described in ICU end-of-life care, including the inability to predict outcomes for individual patients early in their ICU course, the difficulty in assessing patient preferences with the attendant challenges of surrogate decision making, communication problems between families and ICU staff, as well as concerns regarding the adequacy of symptom management for dying patients [24,43,59,62,63]. Wide variability in physician preferences and practices regarding withdrawal of life-sustaining therapies has been described [27,64,65].

A number of recommendations and guidelines to enhance care-delivery for dying ICU patients [45,66–73] are currently being incorporated into instruction in end-of-life skill to a broad range of trainees in and residency and fellowship training programs [74]. Quality indicators for end-of-life care in ICUs include domains of care focusing on patient and family-centered decision making, communication, continuity of care, emotional, practical, and spiritual support for patients and families, symptom management, as well as the creation of support systems for ICU clinicians. Ideally, the future of end-of-life care in the ICU will incorporate a range of validated palliative care-derived principles and allow for the development of a more robust evidence-based structure for the provision of such care.

End-of-Life Decision Making

General principles regarding the ethical framework surrounding decision making in the ICU setting are outlined in prior sections of this chapter. In the United States, there is substantive consensus, as well as legal support, for several ethical principles of particular relevance to ICU practice. These are (i) a distinction can be drawn between acts of killing, and allowing patients to die; (ii) withholding and withdrawing life-sustaining treatments can be considered equivalent; and (iii) the "doctrine of double effect" permits assertive symptom treatment with medications at the end-of-life even if death might be inadvertently hastened (an unintended, albeit foreseen potential consequence of such medication use) [43,75–79].

Patient- and family-centered care is increasingly being viewed as an ideal model for patient care in ICUs, and this naturally extends into the arena of end-of-life decision making as well [43,80,81]. Involving patients' families and surrogates in this process is of obvious importance, given the high percentage of ICU patients lacking decisional capacity [82,83]. A number of factors may influence physicians' attitudes and recommendations regarding end-of-life questions, but most importantly, clinicians must integrate their patients' views and values into a given care plan to establish goals of treatment that meet the needs of patients and families, in addition to being clinically realistic. Communication between all parties involved in a given case is the means to achieve this goal. Effective communication with clinicians is of great importance to family members, and in fact, families may rate a given caregiver's communication skills as equally or more important than their clinical skills [84,85]. Yet, despite the importance assigned by families of critically ill patients to communication issues, data suggest that ICU caregivers frequently fall short of family expectations in this regard [31,74,84–86].

A variety of strategies for improving end-of-life communication have been evaluated, and there is an evolving set of recommendations for the conduct of clinician-family conferences in the ICU [34,36,38,43]. In general, clinicians should focus on spending more time listening to families during conferences, acknowledge and address families' emotions, as well as encourage questions from family members. The use of the mnemonic VALUE during family meetings has been examined as a tool for the conduct of these meetings, and there is data suggesting that such structured approaches to communication not only facilitate real-time communication, but also reduce psychological morbidity of ICU patients' families [38].

The largest issue for all parties involved is ultimately the *content* and *focus* of these discussions, namely, how best to

meet the needs of a given patient. For families, the acute onset of life-threatening critical illness may be a singular, unprecedented event, whereas ICU staffs encounter death and dying on an almost routine basis. Therefore, it is of particular importance to consider communication an ongoing, dynamic process with a timeline that will vary from case to case, as families grapple with the need to fathom the patient's wishes (if not explicitly known) in addition to dealing with their own responses to a given situation. Clearly, there is no universal "blueprint" to delineate how to best guide patients, families, or surrogates through the process of decision making in the ICU, as every individual case has unique aspects. Conflict may arise at any point in a patient's care, and it may occur among members of the care team, among family members, or between the clinicians and family members. Timely, open, and honest communication may be the best strategy to avoid or ameliorate such conflicts, although on occasion outside agents may need to be engaged for mediation (e.g., ethics committees).

Changing Treatment Goals at the End of Life

The perspective that intensive care and palliative care are incompatible with each other is being replaced by the opinion that the need for restorative and palliative care coexists along the illness trajectory, with varying emphasis being placed on one versus the other as treatment goals are re-defined [80,87,88]. Once a decision has been made to forgo further curative treatment endeavors, any treatment or intervention ought to be scrutinized regarding its potential to advance the goal of maximizing comfort [89,90]. In general terms, the needs for pain relief, freedom from anxiety and agitation, relief of dyspnea, and the provision of spiritual support, if desired, become the predominant focus of care [90,91]. Ideally, clinicians should explore individual circumstances and adjust their approach on a case-by-case basis as needed.

Withdrawal of Life-Sustaining Treatments: Practical Considerations

Prior to the withdrawal of life-sustaining treatments, clinicians must inform the patient (if interactive) and the patient's family/surrogates about what to expect during this process. They need to be reassured that the patient's comfort will determine medication administration and the tempo with which the withdrawal process occurs. Family members and friends must have as much access to the patient as needed, and can be encouraged to participate in caregiving to an extent commensurate with their abilities and desires. The ICU staff should attempt to modify the patient's immediate environment to create as peaceful a setting as possible. Any unnecessary equipment, monitors, tubes, drains, and lines should be removed. The withdrawal of mechanical ventilation is unique in that its abrupt cessation can potentially cause suffering. Interventions such as pacemakers, defibrillators, vasopressors, intravenous fluids and nutrition, renal replacement therapy, as well as any medications that do not further the goal of maximizing comfort should therefore be discontinued prior to ventilator withdrawal. The cessation of artificial nutrition and hydration at times raises concerns for clinicians and families alike, potentially for a multitude of reasons [92]. Thirst, for example, may be a concern that can be managed without enteral or parenteral hydration by ice chips or other methods moistening the mouth [93]. Despite such concerns, there is little evidence to suggest that the maintenance of artificial nutrition and hydration contributes to a dying patient's comfort, and it may in fact be associated with complications (e.g., feeding tube malfunction, unintentional dislodgement, nausea) [93–95].

As these initial steps are taken, the patient must be closely observed for any signs of distress, such as grimacing, tachycardia, hypertension, accessory muscle use, sweating, and restlessness. Such symptoms can be treated with opioids (for relief of pain and dyspnea) and sedatives (e.g., benzodiazepines), often in combination. Clinical practice guidelines for the use of sedatives and analgesics in critically ill patients have been devised, applying to patients who are expected to recover, as well as those who are dying [91,96]. Clearly, the situation of the dying patient differs from that of the patient for whom curative therapies continue, but some common themes remain. Systematic symptom assessment with documentation and individualized medication administration is of utmost importance. Once the patient is comfortable, ventilator support can be withdrawn. This can occur either by immediate extubation of the patient, or through a process of gradual reduction in ventilator settings. Either approach is acceptable, assuming that clinicians use anticipatory medication dosing appropriate to the change in level of patient comfort that is predicted in response to a given intervention. In actual practice, a range of physician preferences has been reported [97]. Whether or not to ultimately extubate the patient (if the weaning approach is employed) depends on a variety of factors, including the patient's and/or family/surrogates preferences and airway considerations (e.g., edema, volume of secretions), among others.

Systematic investigation of clinical practice and patient preferences has improved the care of ICU patients. The studies cited above have our enhanced ethical reasoning and decision making for patients during all phases of their ICU care.

AN ETHICAL GUIDE TO RESEARCH

Clinical research involving critically ill persons is necessary and poses important ethical challenges. Significant research efforts in critical care medicine have enabled clinicians to improve outcomes and quality of life of those lives saved. Although the ICU remains the ideal environment to evaluate the effects of novel therapeutic agents and cutting-edge technologies, clinical research in this setting raises considerable ethical challenges. We continue to apply ethical principles to support the risks, benefits, and possible burdens of research protocols, yet many legal and ethical aspects of critical care research remain ambiguous. Ethical issues elicited by research require an acceptable balance of benefit and risk, the requirement for clinical equipoise, and the requisite for a valid informed consent process [98]. Nonetheless, concerns about the clarification of the boundary edge between research and clinical care continue to exist, with ethicists debating approaches that may help subjects better recognize the distinction between research and treatment [99]. This failure to understand which parts of ICU activity is research constitutes the *therapeutic misconception* [100] and may result in an overestimate of research benefits and an underestimate of risks. The next section discusses contemporary issues challenges encompassing research and medical ethics in the ICU.

ETHICAL PRINCIPLES APPLIED TO RESEARCH

Research involving critically ill persons is governed by ethical principles. In response to flagrant exploitation during human experimentation in the course of the World War II, The Nuremburg Code set standards for medical experimentation

on humans, establishing that voluntary consent of the human subject is absolutely essential. Subsequently, the Declaration of Helsinki asserted a voluntary consent requirement, and further affirmed that participants in research must possess the right to self-determination (choose to participate) and the right to make informed decisions regarding participation in research, both initially and during the course of the research [101]. The Belmont Report in 1979 articulated the boundaries between research and clinical practice, and identified the principles of autonomy, beneficence, and justice as the ethical underpinnings of ethical research [1]. Defining the boundaries between research and practice, the Belmont Report stated that *practice* refers to interventions intended to better the well-being of a patient and that these interventions have a likely expectation of success, whereas the term *research* was defined as activity designed to test a hypothesis, allow conclusions to be made, and therefore contributes to generalized knowledge. Three basic principles were described, including respect for persons (autonomy), beneficence, and justice. Applying these principles into practice and at the same time adhering to federal regulations, researchers must execute these concepts in an unbiased fashion and with proper clinical judgment to protect the interests of the research subject and assure the integrity of a study.

Autonomy

The informed consent process is an application of the principles of autonomy, with features highlighting disclosure, comprehension, voluntariness, and competence in making a decision to participate in research. The first principle, autonomy, or the right to render independent decisions, requires that the researcher discuss the trial fully in terms that the subject or their designee will understand the process of informed consent and will protect those persons unable to make an informed decision [82]. During these discussions, study risks, procedures, benefits, alternative treatment options, and study-related questions are reviewed. The informed consent process should document understanding and agreement to study participation by a subject who is competent and independent. Ongoing communication with the subject or their designee during the trial is necessary to maintain informed consent and avoid potential conflicts.

Beneficence

Beneficence in research differs from beneficence in clinical care since the actual benefits of research procedures are frequently unknown. Many participants in research trials remain unaware of study design implications, including the possibility of random assignment to a placebo control or comparison group. Although some subjects may participate in research to promote societal benefits, most enroll to achieve direct benefits [102]. Potential study participants may believe they will receive the treatment that is best for them rather than what is best for science. This perception of benefit could inadvertently induce subjects to enroll in research. Consequently, the investigator must attempt to challenge the "therapeutic misconception," the mistaken belief that the research will directly benefit the subject, which draws subjects to research trials. To do so, the investigator must clearly define benefits (if any) and risks, and the study must be monitored for occurrence of anticipated and unexpected risks.

One commonly accepted ethical requirement of randomized controlled trials is uncertainty or equipoise about the interventions being compared. Clinical equipoise [103] ensures a genuine parity in terms of benefit, harm, and uncertainty between therapeutic interventions that subjects would receive as part of clinical practice and the associated potential risks of nontherapeutic interventions (research) of a clinical trial [104]. Investigators should always inform subjects or their surrogates of the difference between an established therapeutic intervention and a nontherapeutic research intervention.

Justice

The principle of justice in research deals with who should receive the benefits of research and who bears the burden. These risks and benefits should be shared equally among all eligible patients in our society. Recruitment of both underserved and underrepresented groups assure each participant's ethical participation in research trials as well as securing the practical objectives of recruiting and retaining a wide range of study participants so as to ensure that the results from clinical trials are generalizable to larger populations. It is the investigator's responsibility to ensure that each subject fully comprehends the study, inclusive of any man, woman, or minority that speaks or reads a language other than English.

Informed Consent for Intensive Care Unit Research

Informed consent is an essential prerequisite for most human trials and is a process for patients and the research staff to come to a common understanding about the uncertainties of the research trial. The five elements of informed consent [82] require the following:

1. The person consenting must be competent in making medical decisions.
2. The information relevant to the person and his or her situation must be disclosed.
3. The person consenting must be able to understand the information.
4. Consent must be voluntary and free from undue influence or coercion.
5. The person must authorize treatment in a clinical investigation.

Because patients are frequently unable to give their own consent, and ICU research is often complex and unfamiliar, it is more difficult to fulfill the five elements of consent for research on ICU patients than for most other groups of patients. Legal experts and ethicists have continually emphasized the importance of transmitting information to potentially participating subjects during the entire process of consent. This process also requires several evaluations including the assessment of the decision-making capacity and competence of the prospective research volunteer. The ability of individuals to incorporate the information needed for providing effective informed consent must be established by assessment for decision-making capacity [105]. The decision making capacity doctrine refers to determination that the potential participating subject has the following abilities:

1. Possesses a comprehensive understanding of the study objectives relevant to the decision to volunteer;
2. Has the ability to weigh the possible risks and benefits of the study and alternative options to participating in a study;
3. Reasoning ability to incorporate the information with personal priorities, values, and consequences;
4. Awareness of their (subject's) right to withdraw from a trial at any time.

Decision-making capacity is generally interpreted to be task specific. That is, a prospective subject may make an informed

decision about participating in a trial involving a simple procedure, but not a more complex process. As an illustration, though a potential subject for a trial may be judged legally incompetent to manage their financial affairs, they may maintain sufficient decision-making capacity to make meaningful decisions about participating in a clinical study or choice of medical treatment. A variety of assessment scales (i.e., mini mental state exam) may be employed to determine decisional capacity; formal and less formal assessments are allowable and the relevancy of the exam will depend on the specific research protocol to be done [106]. When prospective participants are temporarily incompetent or lack decision-making capacity due to serious illnesses, either the subject cannot be enrolled or a designated surrogate can provide consent.

A barrier to enrolling ICU patients in research studies is the information that must be provided to obtain consent. Studies of the consent process show that patients and surrogates frequently fail to understand consent documents, and many cannot distinguish between research and routine care [107]. At the center of the issue is a fundamental conflict between two components of informed consent: full disclosure of relevant information, and understanding of the information by the prospective participant of the study. With the scientific language and complexity of clinical trial methodology, it is highly likely that most participants with insufficient skills will have difficulty totally understanding the study's objective(s) and the consent form. Moreover, when developing an informed consent document that enhances readability, simplification of the document may unintentionally render it ambiguous or perhaps too appealing. Though informed consent documentation is essential to obtain, time spent in conversation with prospective study subjects to assist the subject in better understanding the research project is vital. Informed consent is not only a brief discussion to obtain a signed document, but is a process that continues throughout the clinical trial. Consequently, improving the consent process is an important challenge to the immediate future of critical care research.

SURROGATE CONSENT

Federal regulations for the protection of human subjects defined under the "common rule" state that "no institution may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent from the subject or the subject's legally authorized representative" [108]. The term *legally authorized representative* (LAR) may be interpreted specifically to mean a court-appointed guardian, or more broadly to mean individuals who are authorized under state law or rules of the institution to serve as a proxy decision maker for clinical decisions. Consequently, all research trials must require that surrogate consent be obtained from the subject's legally authorized representative/surrogate decision maker in conditions of critical illnesses in which potentially effective therapies or research interventions need to be initiated within a specific time frame and that documentation of the presence of cognitive impairment, lack of capacity, or serious life-threatening diseases and/or conditions of the prospective subject exists. Currently, most institutional review boards (IRBs) in the United States with laws that sanction surrogate consent for overall medical treatment permit family members to serve as LAR for research. Surrogate consent for participation in a research study should be employed to the extent that it is consistent with the intent of the Common Rule 45 CFR 46, (Subpart A) and all other federal and state laws pertaining to the protection of human subjects participating in research [109].

One approach to recruit patients in studies, while simultaneously preserving sound ethical research and patient autonomy, is to include employing a consent option [110], whereby surrogate consent is initially obtained to enroll a patient in a trial, and the consent process is repeated (continuing consent) when the subject regains competence. This consent option allows a patient to refuse continuing participation but can preserve important collected data.

Some acute care research can proceed under a waiver of informed consent for interventions that may be medically necessary or require emergency treatment. In 1996, federal regulations established a policy for a waiver of informed consent for a limited class of research in human subjects who require emergency therapy and due to the subject's medical condition and the unavailability of a LAR, no legally effective informed consent can be obtained. This amendment (21 CFR 50.24) [111] permits a waiver of informed consent so that the patient may become a subject in a random assignment emergency research project that may include a placebo arm. Under the terms of the waiver, consent would be waived in certain life-threatening circumstances, including: the person requiring emergent action to save his or her life; the person is not capable to provide informed consent as a result of the condition; a surrogate is not readily available to obtain consent within the clinical trial window; the available therapies are unproven for this life-threatening condition; or the collection of scientific evidence is appropriate and necessary to evaluate safety and effectiveness of a particular intervention. A recent survey indicated that a majority of those surveyed concur with the potential benefit of allowing subjects to participate in an emergency research study without prior consent. Yet approximately 30% of persons would not be willing to choose to participate in emergency research or provide consent for their family members despite knowledge about the process [112].

INSTITUTIONAL REVIEW BOARD

Local review boards (IRB) at each institution in the United States represent one essential component of the multiple protections for research subjects. IRBs are overseen by the Office for Human Research Protections (OHRP), the agency responsible for evaluating local IRB compliance with federal regulations for protection of human research subjects, and by the Food and Drug Administration [113]. IRBs assure that research protocols are conducted ethically, that the research question is potentially beneficial and scientifically sound, and that risks to the subjects are minimized. In practice, much of the focus of an IRB review is the adequacy and accuracy of the information provided in the informed consent document to permit potential subjects to understand risks and procedures in a research study.

Individual IRBs have latitude to interpret and apply the federal regulations. The process of approving research protocols differs among institutions and may be attributable to state and local practice (laws, institutional polices, professional, and community standards). Variability in approving IRB research proposals can also be due to differences in the interpretation of the federal regulations [114]. It may be necessary for the OHRP to clarify regulations if IRB decisions deviate from the original intent of federal regulations. Review of multicenter clinical trials by a central IRB is another method to reduce unwarranted variations among IRBs and to also address ambiguities of the federal regulations.

QUALITY IMPROVEMENT INITIATIVE OR RESEARCH?

In recent years, quality improvement (QI) initiatives have become more interventional and are often tied to

cost-containment efforts. Review of the federal definitions of research related to typical QI activity suggest that much QI activity should be categorized as research because it may not benefit the patient and may represent a potential burden or risk. Without informed consent, much QI activity could be considered a violation of the principles of the Belmont Report. The purpose of QI activity is generalizable knowledge, but defining when this is research is difficult. Casarett et al. [115] suggest that a QI intervention is appropriately called research if the research subjects need protection as the patients involved in the project are not expected to benefit from the knowledge gained and are subjected to additional risks beyond usual clinical practice. Bellin and Dubler [116] concluded that studies using a control group are considered research; projects that carry minimal risk (data collection) are more readily characterized as not research, whereas riskier projects require independent review. Generally speaking, quality improvement initiatives are not anticipated to have any application beyond the specific organization in which they are conducted. If the goal of the project is to evaluate the accomplishments of an established program and information acquired from the evaluation improves a local program, the activity should not be deemed as research activity. On the contrary, when a quality improvement project involving human participants is testing a newly modified or untested intervention or program to establish its effectiveness and is applicable elsewhere, whether in published form or not, this activity would be considered human participant research and subject to IRB review. QI research has recently been addressed by the OHRP in response to a quality improvement research project seeking at reducing catheter-related infections in 103 ICUs at 67 Michigan hospitals [117]. The initial OHRP conclusion that the initiative constituted human subjects research requiring IRB review was based on the doctrine that informed consent was necessary for quality improvement research involving multiple centers. Given that informed consent for this study evaluating a protocol designed to routinely implement five evidence-based procedures could not have been obtained, does the absence of consent violate any important infringement of patient autonomy? A further review by the OHRP concluded that the initiative was being used solely for "clinical purposes and was not considered medical research or experimentation" [118]. In this specific case, the quality improvement interventions were not experimental but rather safe and demonstrated compliance with evidence-based procedures. Accordingly, patients were not rendered to be at greater risk than that provided by routine clinical care. Further discussions are warranted to reach consensus on the ethical and regulatory viewpoint to waive informed consent for low-risk research where the logistical situation may not allow for consent to be obtained, and consent would not necessarily offer significant protection for subjects.

HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT

The Health Insurance Portability and Accountability Act (HIPAA) regulations established a federal minimum on the protection of patient privacy [119]. HIPAA regulations mandate appropriate confidentiality safeguards for medical records research without subject authorization. Recent proliferation of electronic health records and computerized research of these records have raised concerns about privacy of health information. Some argue that informed consent should not be required for research of databases because of the potential benefits to society, the minimal risks to the patients involved, and the impracticability of obtaining consent from all patients. One approach is to acquire a limited dataset, omitting information that might permit patient identification. An IRB may authorize a waiver of consent under specific regulations including when a study intervention is minimal risk (e.g., collection of routine data) and does not alter routine care. The rationale for study without consent is that the research involves minimal risk to the subject and these patients would consent if they could be informed, the waiver will not adversely affect the subject's rights and welfare, the research could not be performed without a waiver, or the subjects will eventually be provided with additional relevant information after participation. In our publicly funded health system, patients have a social obligation to allow their de-identified health care data to be used without their consent so that the health care system can be monitored and benefit all. For certain data registry subcomponents such as collection and storage of biological samples and direct patient interviews, consent should be obtained. Some critics suggest that the HIPAA regulations or restrictive interpretation of these regulations will lead to further barriers to clinical research, diminish the volume of research, and discourage institutions from making medical records available for research. In one national survey, HIPAA, researchers reported that privacy rules have added significant costs and delays to the conduct of research in the United States and negatively influenced the conduct of clinical research [120].

SUMMARY

Decision making about goals of critical care, end-of-life care, and participating in clinical research is influenced by a long history of ethical reasoning, legal judgments, and clinical considerations. The evolving practice of shared decision making for critically ill persons is being shaped by our understanding societal values and the impact of ICU care on patients and their families.

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CHAPTER 212 ■ ASSESSING THE VALUE AND IMPACT OF CRITICAL CARE IN AN ERA OF LIMITED RESOURCES: OUTCOMES RESEARCH IN THE INTENSIVE CARE UNIT

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During the last three decades, critical care has matured to a distinct medical specialty. Sepsis, respiratory failure, and the care of the complicated postoperative patient are now perceived as the purview of the intensivist. Concomitant with this evolution in critical care medicine has been a growing focus on health care outcomes. This emphasis on the end points and effects of medical care generally and critical care specifically reflects the realization that critically ill subjects face a high risk of death and that many interventions applied in the intensive care unit (ICU) are expensive. Some older studies estimate that nearly 1% of the gross national product of the United States is consumed in the ICU and, relative to days spent on hospital wards, others suggest that ICU costs are nearly three times greater [1,2]. Whether it is mechanical ventilation (MV), extensive nursing care, or acute dialysis, many of the technologies and medications used in the ICU are associated with substantial economic costs. In addition, many often perceive that ICU interventions only delay mortality rather than prevent mortality, or that mortality reduction in the ICU comes only at the price of significant morbidity. Thus, there is increasing pressure to carefully evaluate and to understand the results of ICU care. This pressure becomes even more evident when one considers that ICU outcomes must be evaluated from both patient and societal perspectives. In other words, the emphasis on outcomes in the ICU reflects an underlying question about value.

Outcomes research reflects a systematic effort to address these issues and concerns. According to a recent position statement on outcomes research in critical care, "Outcomes research is employed to formulate clinical practice guidelines, to evaluate the quality of care, and to inform health policy decisions" [3]. Like clinical critical care, outcomes research draws on many different tools and expertise in multiple disciplines. More than only an issue of economics, outcomes research requires expertise in psychology and anthropology (to understand patient and physician behavior), epidemiology (to identify disease patterns and burdens), and health services research (to appreciate process) [3]. Use of a term like *outcomes*, though, presupposes a question: Outcomes for whom? At the bedside, the clinician or the investigator focuses on pathophysiology of a sole patient. Outcomes research addresses broader issues. Rather than being either centered on a particular disease or a physiologic measure, outcomes research deals with the overall results of care for the patient, for the family, and for society. Also in distinction to traditional clinical research, outcomes research has clear policy aspects as well; it attempts to facilitate debates about competing plans for resource allocation, research priorities, and national health policy. As an example, a randomized clinical trial deals with issues of efficacy (Does intervention "*x*" in a controlled environment have an independent impact?) and outcomes research is more concerned with effectiveness (What are the implications of intervention "*x*" applied outside a controlled setting and in the "real world" for the patient and society?). Traditional clinical research, moreover, often employs experimental approaches, and observational methods are routinely used in outcomes research. In short, outcomes research attempts to use methods from the social sciences to augment the understanding of health care as opposed to using only methods from conventional "hard" sciences. As a recent summary regarding outcomes research in sepsis indicated, the outcomes researcher seeks to answer a question separate from traditional research [4]. The clinical investigator essentially asks, "Does this work?" and outcomes researchers deal with the concern, "Does it help?" [4].

Readers should note that outcomes research is now a key component of the biomedical enterprise. It is no longer seen as an option or an add-on. It fits with mechanistic and clinical work in building the triumvirate of information needed to translate research findings into clinical practice. The absence of outcomes studies can lead to the failure to adopt what otherwise might be useful interventions.

METHODS IN OUTCOMES RESEARCH

Outcomes research relies on multiple methods for exploring patient-centered concerns. Generally, researchers employ both qualitative and quantitative methods [3]. Qualitative approaches are only occasionally used but can offer insight into complex processes that do not easily lend themselves to standard hypothesis testing. As such, qualitative work often results in the generation of important hypotheses for more formal testing. Quantitative methods are more standard in outcomes research in critical care and have two general aspects. First, they use some tool to measure a particular outcome (e.g., mortality, quality of life, functional status, cost). Second, quantitative techniques then seek to compare the outcome of interest between at least two alternatives. Unlike the controlled environment of the bench laboratory or even the randomized controlled trial (RCT), outcomes research is necessarily exposed to multiple potential confounders that can and do affect the primary measure of interest. Because critical care outcomes research remains patient-centered, it is important to acknowledge that these subjects bring with them complexities that may alter their mortality, quality of life, and function. Moreover, the impact of these preceding factors may affect a researcher's end point of interest in ways that have little to do with the

intervention under study. Similarly, after any intervention in the ICU, many post-ICU variables come into play that might affect the results of an outcomes study.

To address these complexities requires adoption of various techniques, all of which must be rigorous and reproducible. Therefore, outcomes research relies on more than simply RCTs. RCTs are well suited for deciding if specific interventions or agents can alter an easily ascertainable end point such as mortality. For example, use of large sample sizes combined with both block randomization techniques and protocols for patient care help to ensure that the potential confounders previously noted are minimized and, in turn, allows one to explore questions such as how low tidal volume MV affects mortality at day 28. But if the policy or research query deals with the functional status or total cost of care for survivors of acute respiratory distress syndrome (ARDS) more than a year after their hospital discharge, one may require additional approaches other than an RCT. In any event, critical care outcomes research begins by defining a particular question. The investigator can subsequently determine which approach is most appropriate.

In fact, sometimes outcomes research requires entirely separate study designs and major modifications to traditional models of clinical research. In other cases, more traditional models of investigation can be expanded to incorporate outcomes measures. This generally requires building these measures into the trial during the study inception phase. Therefore, outcomes research can be seen as an extension and complement to standard research practices. In other areas of medicine, such as rheumatology, patient-centered measures such as quality of life have come to serve as the primary end point in clinical studies.

Observational Studies

Of the various types of observational studies (e.g., case series, case-control, cross-sectional, and cohort), two are particularly important in critical care outcomes. A cross-sectional design has the advantage of looking at one precise time or over a short period of time at a specific disease or practice. This snapshot-in-time approach can provide important insight into both epidemiology and health services research. For example, a recent 1-day international survey of respiratory failure in the ICU demonstrated the burden of this disease relative to other diseases treated in the ICU and also documented the wide range in practice style with respect to the use of MV [5]. The Sepsis Occurrence in Acutely Ill Patients (SOAP) study, a European sepsis registry using an essentially cross-sectional design (it covered a set 2-week period) confirmed the burden of sepsis in the ICU and underscored the variability in the use of various medical therapies in the care of these patients [6]. Hence, these cross-sectional analyses generated important information about the current state of affairs and therefore provided a potential benchmark for use in future comparisons.

In addition, cohort studies are valuable components in outcomes research. With this strategy, subjects are selected based on some common characteristic (e.g., a diagnosis, a risk factor) and then observed [7]. Thus, cohort analyses have the advantage of being prospective. Cohort studies also specify a set starting time for the observation (e.g., time zero) from which observations proceed forward. Researchers can then look at the interplay of certain predefined risk factors or interventions and the characteristics that defined the cohorts to see how these affect the outcome. Often a cohort design is used to either describe the natural history of a disease or to assess quality of life. Although theoretically straightforward, cohort studies pose important challenges to the researcher. Selection bias and the inherent heterogeneity of critically ill patients can confound efforts to create a homogeneous cohort. Similarly, one needs to ensure means for capturing multiple potential exposure variables and acknowledge that the interaction between risk factors, exposures, and time is complex.

As Needham et al. [7] and Dowdy et al. [8] indicate in a recent review of methodologic issues associated with cohort studies, this study design has three key components: subjects, outcomes and exposures, and time. Subjects must be carefully identified, but the cohort study gives the researcher flexibility to define the population as sharing particular characteristics, such as common diagnoses, or risk factors. Alternatively, cohorts can be developed such that two groups emerge: individuals exposed to a particular event or variable and those not exposed. As a result, one can, using this technique, begin to draw conclusions about causal relationships. Generally, because the cohort shares some common time of designation (e.g., time zero) by observing the population one can evaluate the strength of the relationship between the given exposure and the outcome. Unlike the rigidity of an RCT, in which randomization works to ensure study groups are similar except for the intervention in question, a cohort design provides the researcher the chance to explore multiple exposures simultaneously, and how they interact with each other. To the point, in an RCT of a novel treatment for sepsis, any differences seen in outcomes should be a function of the particular intervention experimentally introduced. The ICU organization, pre-ICU care, and posthospital events should not affect the outcome because randomization should ensure that the impact of these variables is equalized between the active and comparator groups.

The purpose of a cohort study is to enhance the RCT by providing information that cannot, by definition, be gleaned from the RCT. Expanded adoption of cohort studies can also facilitate better understanding of natural history by shifting the focus back to a time prior to ICU admission. Without some initial work with adopting a cohort approach, we cannot hope to address significant questions relating to what determines which patients get admitted to the ICU, who most likely benefits from ICU care, and the outcomes for those never admitted to the ICU.

INTERVENTIONS AND END POINTS IN CRITICAL CARE OUTCOMES RESEARCH

Unlike traditional biomedical research, which looks at either novel technologic interventions (new drugs, new devices) or perhaps management strategies, the interventions studied in outcomes research are more diverse. Certain clinical measures have significant outcomes implications for the patient and society. However, managerial and organizational changes may be equally important. The issue of management and organization of critical care services is particularly acute at present, given current (and conflicting) data suggesting that the model of ICU administration affects both mortality and cost [9,10]. The question of organization and management is broader than simply whether one uses a closed, full-time intensivist model or a more traditional open ICU model. Under the rubric of organization and management are questions of nurse-to-patient ratios, the role for respiratory therapy, and the value of a dedicated critical care pharmacy group. Measuring how these types of potential features of the ICU work and whether they help patients and society is perhaps as important a question as if a new molecule for sepsis alters mortality. Issues of management and organization can provide feedback to affect the conduct of traditional research. Whether it is studies of resuscitation strategies or rapid response teams, these types of interventions

include service, delivery, and organizational aspects. If any one of these components of the trial collapses, the entire venture may be jeopardized.

Mortality

With respect to end points, mortality remains the center of investigative efforts because it has tangible meaning to the patient, to health care institutions, and to society. When outcomes research addresses mortality, it tries to do it in an appropriate context. In other words, the question of mortality begs the question of when? Is the appropriate timeframe survival to ICU discharge or to hospital discharge? Are these time points too myopic? Altering long-term mortality (e.g., 2 years after ICU admission) would be an admirable goal. Historically, 28-day all-cause mortality has served as the primary end point for trials in critical care. However, after some period of time it seems reasonable to postulate that occurrences and interventions in the ICU diminish in their impact while the patient's age [11] and health state prior to his or her ICU admission [3] become the main drivers of outcomes. Thus, the issue revolves around the timeframe chosen for measurement and its likely mechanistic link to the intervention under evaluation [12].

It is important to be cautious, though, since one can artificially alter ICU mortality by early use of certain interventions (e.g., tracheotomy in order to facilitate transfer to a chronic ventilator care facility). Likewise, decisions about when to suggest withdrawal of care can alter the apparent timing of death in the ICU. The central limitation is that with all time-dependent end points, there can be confounding by multiple factors. As the recent American Thoracic Society position statement on outcomes research appropriately observes, "The 'correct' mortality endpoint depends on the specific research question, the mechanisms and timing of the disease and/or treatment under study, and the study design" [3]. In addition, if a disease state is not associated with significant mortality, use of this measure may simply fail to capture the value of a particular intervention. Finally, mortality as the sole end point of any research ignores the entire concern about morbidity and the tradeoff between mortality and morbidity. Similarly, it fails to address the quality of life of the survivor.

Mortality, moreover, has limitations as a tool for comparing outcomes across different ICUs. Although recorded and tracked nearly uniformly in ICUs throughout the world, ICU mortality is a relatively uninformative measure of ICU performance. Extensive variability exists in not only the types of patients admitted to different ICUs but also in admission and discharge policies [12]. Some ICUs serve as major referral centers for and receive multiple transfers from other hospitals. These patients tend to be sicker or in need of specialized care. Hence, the mortality rates of the ICUs that send these persons elsewhere may be artificially low compared to the ICUs that accept such high-risk cases. Similarly, ICUs with intermediate-care facilities can transition individuals out of the ICU at different rates than ICUs lacking access to these resources. This fact can alter apparent ICU mortality rates because one might essentially be able to transition patients receiving comfort care only out of the ICU so that when they die the death is not captured as an ICU-related event.

One could correct for these possible variables by employing a definition of ICU mortality (for benchmarking performance) that removed transfers from both the numerator and denominator of the crude mortality rate. Adjusting for differences for availability of "stepdown" wards can be made by limiting comparisons to like-sized hospitals. However, even these efforts would be insufficient for purposes of performance and quality assessments because issues of case-mix remain unaddressed. Case-mix as a concept tries to capture that different ICUs admit different types of patients with differing severity of illnesses. It is important to note that case-mix as a concept describes more than differences in disease severity [13]. Case-mix adjusting tries to balance issues with underlying diagnosis, comorbidity, age, and severity of illness [13]. To illustrate the breadth of the aspects related to case-mix one need only consider an ICU that cared for only postoperative cardiothoracic patients should report low mortality rates and an ICU that admitted mainly immunocompromised persons would certainly describe different outcomes, even after one adjusted for severity of illness. As a corollary, comparing mortality between similar types of ICUs that admit similar types of patients, after controlling for disease severity, can prove helpful [13].

Severity of Illness Tools

To address disease severity, multiple tools exist. They differ with respect to the variables they measure, when they measure these variables, and if they try to describe ICU mortality or hospital mortality. The Acute Physiology and Chronic Health Evaluation (APACHE) score is commonly used in the United States and the Simplified Acute Physiology Score (SAPS) system is more regularly employed in Europe [14–16]. Severity of illness scores have been developed for application in specific types of patients (e.g., pediatrics, trauma) and others try to deal with a broader range of subjects. Other modeling systems include the Sequential Organ Failure Assessment (SOFA) score and the Multiple Organ Dysfunction Score [17,18]. A major limitation of all scoring systems is that they are developed and validated on large patient populations. Therefore, predicted mortality estimates for individual patients cannot and should not be translated into decisions at the bedside as to whether, based solely on predicted mortality, one should withhold or offer aggressive care.

Another concern with severity of illness tools as they relate to mortality is that some were initially created many years ago. Over time, new interventions and technologies have altered patient care and morality. Hence, older iterations of certain models may not longer apply and no longer have adequate calibration to be informative. Like many scales, they require recalibration. As an example, the APACHE system is now on its fourth revision, and with APACHE II versus APACHE IV, there are significant differences in terms of the explanatory power [19]. Nonetheless, in critical care research many have adopted the APACHE II and III approach as its equations are published. Researchers and administrators need therefore be cautious when assuming that similar scores computed by an older rubric necessarily translate into similar predicted mortalities among populations or across ICUs. APACHE generally functions by exploring historical cohorts of patients and creating prediction scores based on this "control" population. Alternatively one can also use the acuity measures used in these instruments to derive from predictions that are specific for the population of interest or under study.

Calculations of the actual scores for patients can also be prone to error. Several studies document significant interobserver variability among even trained researchers as to the calculation of severity of illness scores [20]. With APACHE II, one project revealed that the interrater agreement was strikingly poor ($\kappa = 0.20$) [21]. The main sources of variability appeared to be in assessment of the Glasgow Coma Score but variability was evident even in the determination of the blood pressure. Changes in practice can also have unpredicted effects on severity of illness scores. Nearly all scoring systems rest on measurement of physiologic parameters such as blood pressure, platelet count, and hemoglobin. The more extreme the actual value from the "normal" range, the greater the negative impact of this factor on the individual's composite

severity of illness score. As an example, a low hemoglobin is associated with more APACHE II points than a normal hemoglobin. Clinicians, though, may now be more tolerant of lower hemoglobins than they were when APACHE II was created. In fact, a restrictive transfusion strategy that necessarily allows the hemoglobin to drift lower may improve outcomes [22]. Consequently, APACHE II scores may be rising in ICU patients over time, reflecting this change in practice because physicians are not transfusing as frequently. This increase in APACHE II-predicted mortality when actual mortality might improve because of a change in clinical practice based on a large randomized trial underscores a significant assumption and limitation of severity of illness scoring classifications.

Severity of Illness and Performance Assessment

Mortality prediction equations can also result in calculation of a standardized mortality ratio (SMR) [13]. This ratio compares observed mortality to predicted mortality. Conceptually, the SMR can be calculated irrespective of the severity of illness system used to determine the predicted mortality. Ratios greater than 1 suggest excess mortality and those less than 1 imply enhanced survivorship. Implicitly, an SMR greater than 1 indicates an ICU with inferior outcomes after adjusting for severity of illness case mix. Alternatively, though, differences in SMR can reflect more than quality. First, scoring systems may be generally imprecise (see previous discussion) and may not capture some aspects of disease severity or other case-mix issues. Second, the SMR can be affected by the quality of data collection and by the sample size. There is also discordance in the published literature exploring if and how well the SMR correlates with other markers of ICU quality. Some investigators suggest the SMR sufficiently captures aspects of quality and others conclude that the relationship between other markers of quality and the SMR is less clear [13]. It is likely that no one SMR calculation method accurately reflects quality. Therefore, as policy makers, third-party payers, and patients demand simple report cards that allegedly capture quality, it is important that the intensivist resist the urge to simply publish SMRs without references to case-mix. Some more recent scoring systems address this (i.e., APACHE IV) but still may be imprecise as they derive from historical cohorts. We need to encourage the use of multiple measures beyond the SMR to describe qualitative differences in ICUs.

Nevertheless, the SMR can be used over time to assess interventions within an ICU or group of relatively homogenous ICUs [13]. Although one may not be able to conclude that SMR differences across institutions reflect true differences in quality and performance, when used as a benchmarking tool the SMR can be insightful. If one ICU has historical data about its case-mix and performance, it can then track over time how the SMR varies in response to interventions. Conversely, an increasing SMR can suggest the presence of some change in practice or structure that is adversely affecting mortality. By identifying these trends and investigating them, ICU staff can elucidate potentially harmful changes that have transpired and attempt to address them.

Organ Failures

One effort to move beyond mortality as the primary outcome measure in critical care has been the evolution of the concept of organ failure-free days [3]. The free-day paradigm recognizes that reducing mortality in the ICU may not always reduce morbidity. In fact, reductions in mortality may only increase morbidity by keeping alive for several additional days patients who otherwise would have died but then, nonetheless, succumb to the acute illness. From a different vantage, some interventions may appear attractive on a superficial level because they decrease the duration of either MV or vasopressor support. However, a shorter duration of MV in one population may only reflect a higher death rate in that cohort. In other words, there is a competing impact of mortality in the assessment of such time-to-event (e.g., liberation from MV) phenomena.

These two facts promoted the development of the failure-free day paradigm. As a consensus conference on sepsis stated, this concept evolved out of a need to evaluate "the net effects of therapy" and to try to "integrate mortality with morbidity" [3]. Failure-free days are computed so that each day alive free of the organ failure in question is counted during the specified observation period. If a patient dies before the study termination or requires support beyond this time point, he or she is assigned 0 failure-free days. Historically, failure-free days are measured up to day 28 following the start of an investigation. The 28-day cutpoint, however, is arbitrary and reflects that most trials in critical care use the 28-day mark as the final date for ascertaining vital status. One could follow subjects out further if there were a biologically plausible reason to believe that the intervention under analysis could have an impact to that time point. As an example, if one were interested in MV-free days accrued during the 28 days following a patient's enrollment in a study and the patient died on day 7, he or she would be credited with no ventilation-free days. If the individual required 7 days of ventilation and was alive at day 28, he or she would have earned 21 MV-free days. If remaining on the ventilator for all 28 days, no ventilator-free days would accrue.

The failure-free day approach has the potential advantage of capturing morbidity that transpires outside the ICU, such as the need for continued dialysis, as it is organ system-specific rather than defined purely based on the subject's location of care. It can further account for shifts in a patient's clinical status that might not be measured accurately if a researcher only recorded mortality. A patient with chronic obstructive pulmonary disease, for instance, might require 2 days of ventilatory support initially, be liberated from MV, but then several days later deteriorate and need to be placed back on ventilatory support. This waxing and waning in clinical status can potentially be accurately described from an outcomes perspective with the use of ventilator-free days.

Is it appropriate to pool death with requiring 28 days of MV but still surviving? The fundamental struggle in this question illustrates why organ failure-free days can only be used as an adjunct to other measures of outcomes in critical care. It is certainly not clear that organ failures correlate with meaningful clinical outcomes or if surviving 28 days on a ventilator with a respiratory organ failure is comparable with death. On the other hand, the concept of organ failure-free days allows one to examine if and how a novel approach or therapy might accelerate recovery. In turn, it lays the foundation for the use of pooled end points in clinical trials in critical care. If mortality remains the only primary end point for studies in critical care, then investigators may fail to pursue options that may prove valuable in other ways. The organ failure-free day concept also allows one to capture the effect of interventions on markers of resource utilization and cost. Differences in the use of ventilation, dialysis, and vasopressors have important implications for patients. Simultaneously, because of the costs associated with these interventions, decreasing organ failures and morbidity has ramifications for health care institutions, third-party payers, and policy makers. Future work in this area may in fact move beyond organ failure and try to develop metrics that incorporate this with mortality into a form of quality-adjusted survival measure.

Health Status

From the patient's perspective, surviving the ICU raises many issues. Most patients will require some additional time for further recovery along with the potential need for rehabilitation. Moreover, some physical impairment persists after ICU care, and this impairment can affect functional status, mental health, and quality of life. Globally, each of these concepts (functional state, mental health, quality of life) all attempt to capture the concept of health status. The need for adequate assessments of health status is made more acute given the limitations evident if one has only a sole focus on mortality.

Readers should note that, although the concepts are intertwined, functional status (either physical or mental) is distinct from quality of life [23]. Functional status depicts the subject's capacities and quality of life attempts to gauge an individual's satisfaction and state of well-being. As a result of this subtle distinction, someone who has a major functional limitation may rate his or her quality of life as high while another patient with relatively minor limitations might describe his or her quality of life as poor. Moreover, quality of life essentially relies on using the individual as his or her own control. Persons necessarily rate their quality of life relative to what they perceive it was prior to needing ICU therapy. Functional status, on the other hand, generally measures capabilities relative to a fixed scale of performance that is set irrespective of what the person's prior functional status might have been. As such, functional status tends to be more objective. Quality of life, alternatively, is influenced by a person's values, perceptions, and preferences [24]. Quality of life also is measured in a social context. Assessing an ARDS survivor's lung function provides no insight into how having physical limitations after surviving ARDS alters one's interactions with their family and friends.

Functional status captures physiologic assessments of impairment along with global and mental/neuropsychologic performance. Early outcomes studies in critical care and functional status explored the long-term pulmonary complications of ARDS [25]. Researchers examined how gas exchange and radiographs varied over time in ARDS survivors. Other investigators have used general measures of functional status to describe survivors of ICU care [25]. Often-used tools for this include the 6-minute walk test and the activities of daily living (ADL) system. ADL assessments as a tool have the advantage of being widely familiar to clinicians and easy to implement. Some, though, question their applicability to critical care outcomes [23]. ADLs may be of limited value because they were developed specifically for the elderly. Young survivors of critical illness may recover to a state of function beyond what the ADLs can possibly capture. The information that does exist indicates that severe functional impairment results following ICU care and that it may resolve slowly. For example, Herridge et al. [26], in a prospective observational analysis of ARDS survivors, noted that only 50% had returned to work by 1 year and many reported persistent limitations in their ADLs.

Evaluation of cognitive impairment complements appraisals of functional status. Again, because of the difficulty in assembling cohorts of critical care survivors, the heterogeneity of these patients, and the lack of validated tests appropriate for ICU survivors, limited information exists regarding this as an outcome parameter. In a comprehensive review of this issue, Hopkins and Brett [27] reported that at 1 year nearly a third of ARDS patients had cognitive limitations. A more recent study of a cohort of 51 ICU subjects suggested that 35% of these subjects scored at or below a level similar to the lowest fifth percentile of a normal population [28]. However, over time, 95% had experienced significant improvements in cognitive function [28].

The implications of persistent cognitive impairment are significant because they may portend difficulties with future employment and return to work. Hence, improved evaluations of cognitive recovery after critical illness in clinical trials, and the time course of that recovery, may help identify interventions that can have major implications for our patients. Again, if not incorporated into outcomes research, one cannot determine if and how what we do affects this variable. Likewise, it seems that different approaches to care in the ICU can alter neuropsychologic recovery from critical illness. Specifically, posttraumatic stress disorder (PTSD) is an emerging concern in outcomes research. The incidence of PTSD following an ICU course is unknown, but some survivors report disturbing memories and meet the clinical criteria for PTSD. Outcomes researchers have linked the development of PTSD to previous delusional memories while hospitalized, suggesting that our approach to sedation during the acute phase of a subject's illness can affect the rates of PTSD [29]. Confirming this, Kress et al. [30] observed that the incidence of PTSD approached 33% in persons randomized to standard sedation practices in the ICU and there was no PTSD in those allocated to a strategy relying on a daily interruption of sedation.

Quality of Life

In distinction to functional parameters such as the 6-minute walk distance or even cognitive function, estimating quality of life posses several unique challenges. Determining both the validity and reliability of quality-of-life measures, for example, is difficult. In addition, quality-of-life evaluations represent an intersection of clinical science with social science because many of the tools for rating quality of life rely on psychometrics for their theoretical foundations. Furthermore, the results of quality-of-life determinations can be affected by who is asking the questions and how they are asked. Research documents clearly that a patient and his spouse may score the patient's quality of life differently.

In general, quality-of-life tests attempt to score this on some form of a scale, which may be either continuous or categorical. The survey tool itself is often composed of select items that ask about certain aspects of life, functionality, quality, and so forth [24]. Items that inquire about certain, specific categories or aspects of quality of life are considered to fall within the same domain. Examples of domains routinely used to classify quality of life include pain and impairment, functional status, social role, satisfaction, and death. In reporting the results of quality-of-life testing, both aggregate scores and scores within a certain domain may be reported. The aggregate score often gives a sense of the overall health-related quality of life. Breaking out scores across the various dimensions can presents a profile of how an illness impacts quality of life. In addition, two distinct types of quality-of-life data are regularly collected: health profiles and utility measures [31]. The former generates information regarding the impact of disease and therapies for it on a unique patient. Utility measures, on the other hand, represent the preferences of groups of individuals who share certain common characteristics, such as exposure to like treatments or similar underlying disease states.

Quality-of-life scales may be either generic or disease-specific. Generic scales, such as the Sickness Impact Profile (SIP) or the Short-Form 36 (SF-36), have been developed in large diverse populations so that normal values exist [31]. Using these types of instruments allows comparisons across multiple disease states and various populations. Disease-specific instruments, such as the St. George's Respiratory Disease Questionnaire, may be better calibrated to detect changes over time as they focus on only one disease state or organ system [31]. These disease-specific measures are also focused on aspects of

TABLE 212.1

EXAMPLES OF QUALITY-OF-LIFE MEASURES

Name	Goal	Description	Concepts assessed
Sickness Impact Profile (SIP)	To asses health-related dysfunction	136 items in 12 domains	Physical, psychosocial, other (e.g., sleep, rest)
Short-Form 36 (SF-36)	Survey of general health status	36 items in 8 domains and a summary score	Physical, mental
Nottingham Health Profile	To determine perceived physical, social, and emotional health	Initial part of 38 items and second section of 7 items	Physical mobility, energy, pain, social isolation, emotional
EuroQuol	To measure health state and to determine preferences for 14 hypothetical health states	5 items measured at 3 levels	Physical and mental functioning

Adapted from Chaboyer W, Elliot D: Health-related quality of life in ICU survivors: review of the literature. *Intensive Crit Care Nurs* 16:88, 2000.

quality of life that may be of most concern to that specific group of patients. In other words, there is a tradeoff among rubrics between generalizability and resolution. Therefore, understanding critical care outcomes and ICU care's impact on quality of life necessitates studies using both approaches. Examples of various quality-of-life measures are shown in Table 212.1.

Despite using differing tools, examination of different types of patient cohorts, and issues with follow up evaluation, most quality-of-life research indicates that this is substantially impaired initially in ICU survivors. For example, Tian and Miranda [32] evaluated more than 3,500 ICU patients 1 year after initial admission. Employing the SIP, they observed that scores were substantially reduced among survivors. The main source of the impairment in quality-of-life assessment arose in the area of physical functioning. Interestingly, there was no correlation between the extent of the limitation in quality of life and either severity of illness at ICU admission or the duration of stay in the ICU. Others have confirmed this observation that severity of illness does not explain the limited quality of life reported by some persons. In a cohort of elderly survivors of prolonged MV, Chelluri et al. [33] observed that initial severity of illness as measured by the APACHE III score failed to explain both subsequent functional limitations and lower quality-of-life scores during the year following ICU discharge. Using the SF-36 rather than the SIP, Heyland et al. [34] concentrated on sepsis survivors. Compared to the general U.S. population, scores were significantly lower in nearly all domains. Both physical functioning and social functioning were rated at approximately two-thirds the level noted in a general U.S. sample. However, when analyzed against a cohort of subjects with chronic disease such as either chronic obstructive pulmonary disease or congestive heart failure, the self-reported quality of life of sepsis survivors was similar.

More recent studies have explored how quality of life changes over time after ICU discharge. Most surveys of quality of life represent cross-sectional efforts measuring this at only one time point and therefore provide little information about rates of change in quality of life or how pre-ICU quality of life affects quality of life after discharge. Addressing these limitations, Cuthbertson and coworkers [35] prospectively followed 300 consecutive patients admitted to their ICU. They measured quality of life using two different tools at 3, 6, and 12 months after ICU discharge. At 3 months, quality of life was substantially reduced compared to the subjects' premorbid states. During the ensuing year, quality of life improved and approached the pre-ICU level. Unfortunately, at 1 year, the quality of life of survivors still remained lower than that reported for a general population. Among 109 persons with ARDS, Herridge et al. [26] reported similar patterns in the recovery of quality of life. During 12 months, scores on the SF-36 for physical functioning doubled and those for social functioning rose by 75%.

Several general themes appear in the quality-of-life literature relating to ICU care. First, quality of life is substantially impaired in ICU survivors, but this improves with time after ICU discharge. Second, despite changes in quality of life, this may not return to preadmission levels and the time course of any recovery may be slow. Third, it is unclear what factors contribute to the quality of life of ICU survivors and how interventions in the ICU can affect subsequent quality of life.

Hence, many issues remain unresolved in this area of critical care outcomes research. Plaguing efforts to better comprehend this important patient-centered measure are multiple methodologic issues. As one systematic review of quality-of-life studies concluded: "There is no agreement as to the optimal instrument and [that] differences between studies preclude meaningful comparisons or pooling of results" [36]. These concerns explain why there has been a paucity of work in this area and why one group of investigators observed that fewer than 2% of all articles dealing with general critical care published from 1992 to 1995 dealt with this topic [37]. Despite all these concerns, an expert panel on surviving sepsis endorsed the SF-36 as best suited for outcomes research in critical care [4].

ECONOMIC OUTCOMES

A final aspect of critical care outcomes deals with economic and financial issues. The ICU remains a major focus for concerns relating to cost. Part of this arises from the fact that many expensive technologies are applied in the ICU. Simultaneously, ICU bed days are disproportionately expensive compared with costs related to general ward bed days. Adding to increased cost, sensitivity is a growing demand for ICU care. With the aging of the population, the need for critical care resources will escalate. For example, during the next three decades, the incidence of severe sepsis and septic shock has been projected to rise by 30% [38].

Relative to the entire U.S. economy, it was estimated that, approximately two decades ago, ICU costs accounted for nearly 1% of the nation's gross national product [1]. In a similar analysis, total critical care costs by the year 2000 had nearly tripled from 1984 and now exceeded $55.5 billion annually [39]. As a function of the national economy, however, the proportion of the gross domestic product devoted to the ICU had decreased to 0.56% [39]. Despite this relative fall in the resources consumed by critical care, which essentially reflects the growth of the U.S. economy, the ICU now accounts for one in

seven dollars spent on hospital care in the United States [39]. On a per-day basis, the most recent analyses indicate that costs for the initial day of MV in the ICU exceed $10,000 and fall to $4,000 per day by ICU day 3 when most subjects are clinically stable [2]. In short, from any perspective, whether societal or local, critical care remains exceedingly expensive.

As a result of this economic pressure, patients, physicians, third-party payers, and policy makers are all demanding improved efficiency and optimization of resource allocation. In the United Kingdom, formal cost analyses have become the purview of regulatory agencies, and recommendations from these authorities influence the adoption of new therapies. In the United States, legislation to require formal economic analyses for the approval of new pharmaceuticals is under consideration. Critical care practitioners, therefore, require an appreciation of economics and finance in order to advocate for their patients and the resources they need to care for the critically ill.

A Primer on Economic Analysis

Economic analysis represents a means for understanding and appreciating value in order to facilitate the efficient allocation of scare resources in light of competing claims for those resources. In many scenarios, the criteria employed to determine how to spend limited dollars may not be evident or may be filled with assumptions and bias. The essential goal of economic analysis is to make explicit both the means and criteria used for decision-making. Reflecting the growing significance of economic issues, multiple formal position statements now exist describing both the means to conduct and the implications of financial studies in health care [40,41].

There are several basic varieties of economic analysis in health care: cost-minimization, cost–benefit, cost-effectiveness, and cost-utility. Cost-minimization presupposes that the outcome of interest is fixed and competing approaches are equally efficacious. The main issue, therefore, is which alternative costs less. In critical care, though, few interventions achieve similar results, so a more complex means for comparing options is required. When both costs and outcomes differ, it is necessary to assign the distinct options a value in some common schema (such as dollars). After converting potential results of interventions into dollars, one can proceed with cost–benefit analysis. Cost–benefit analysis is rarely used in health care because many end points are not easily converted into dollar values (e.g., the dollar value of a life) and because cost–benefit approaches may inadvertently assign more value to those who have higher earning potential. Cost-effectiveness acknowledges the limitations of cost–benefit and thus leaves the outcome (or denominator) in clinical terms such that one is now comparing costs per common measure of effectiveness. Often-used examples of this in critical care explore costs per year of life saved or per ICU days avoided. Cost-utility analysis builds on cost-effectiveness analysis by adjusting the clinical outcome for the quality that results from the intervention.

The standard denominator for these types of studies is the quality-adjusted life-year (QALY). The QALY concept acknowledges that a year of life spent in a long-term ventilator facility is not viewed by the patient as being of the same quality as a year lived being fully functional. Although arbitrary, most consider cost-effective interventions that yield a price per QALY saved of between $50,000 and $100,000.

One source of confusion and controversy in economic analysis is estimation of costs. Given the market structure of health care, charges rarely reflect cost. In fact, formal means exist to convert charges to cost based on published cost-to-charge ratios. Analytically, costs can be computed through microcosting, in which the unique costs for each component of care are determined and then summed. Costs can also be estimated based on average bed-day costs. Both approaches have limitations: Microcosting may underestimate the fixed costs associated with care delivery and a bed-day approach assumes that costs remain similar despite the intensity of care the patient requires.

Any conversation about cost, though, has an underlying central question: Cost to whom? This issue of perspective is key in all economic analyses. Some intervention may appear cost-effective to an institution because it shifts costs to a third-party payer. For the payer, though, the intervention will be seen as less than optimal. To address this fact, formal recommendations for the conduct of cost-effectiveness analyses encourage adoption of a societal perspective [40,41]. Utilization of a common societal perspective can also facilitate comparisons across alternatives. However, in critical care, a societal perspective poses specific challenges. As one review notes: "The societal perspective forces consideration of outcomes and costs not usually considered in critical care studies and a time horizon longer than most critical care studies" [13,41].

Uncertainty represents a final aspect of cost-effectiveness and outcomes that merits mention. All estimates for any study's inputs are bracketed by assumptions and uncertainty. The issue then becomes how one's conclusions are affected by this inherent uncertainty. If the costs of an ICU day are half what one assumes, does it alter the outcome of an analysis? Determining the impact of this uncertainty is best done through sensitivity analysis. Sensitivity analysis is a tool for varying a model's inputs across a range of assumptions and seeing if and how the results vary in response to this. If introducing such variability fails to affect the conclusions, one can be more confident as to the strength of the outcomes.

Disease-Specific Costs

Multiple studies in the last several years have attempted to gauge the costs of various diseases commonly encountered in the ICU. These reports help provide estimates of disease-state costs, which can be then used for cost-effectiveness analyses of preventive interventions or be relied on for budget planning.

With respect to nosocomial infection, Warren et al. [42] calculated the attributable cost of a catheter-related blood stream infection (CRBSI) to be nearly $12,000 per event. Their study prospectively followed a cohort of critically ill subjects and compared those developing CRBSIs to those not suffering this complication. In addition, they controlled for multiple potential confounders such as severity of illness, use of MV, and need for dialysis. Blot et al. [43], in a retrospective case-controlled study in Europe, reached similar conclusions. They reported that a CRBSI significantly prolonged the duration of MV and ICU length of stay and resulted in net excess costs totaling € 14,000 [43]. Reflecting these high costs, multiple preventive strategies have been shown to be cost-effective. In an analysis of a multifaceted educational intervention emphasizing the pathogenesis, implications, and prevention of CRBSI, researchers from Washington University demonstrated that their efforts saved approximately $500,000 during the course of a year [44]. Likewise, use of chlorhexidine rather than povidone, adherence to the need for full barrier drapes, and adoption of antibiotic-impregnated catheters have been shown to yield net savings despite their initially high acquisition costs.

Ventilator-associated pneumonia also represents a common and costly ICU-acquired infection. Rello and coworkers [45] observed that the costs of this disease exceeded $40,000 per case. This analysis, though, was limited because it was a retrospective assessment of a large administrative database such that the definition of pneumonia employed might have led to selection bias. Alternatively, Warren et al. [46], in a prospective study of a community ICU, suggested that the costs of

ventilator-associated pneumonia were similar to those reported by Rello et al. Hence, two distinct studies using different approaches reached similar conclusions.

For non-ICU acquired processes, community-acquired pneumonia (CAP) represents a major driver of national health care expenditures by the U.S. government. Describing outcomes in a cohort of patients with severe CAP, Angus et al. [47] suggested that persons with CAP needing ICU care generated total hospital costs in excess of $21,000. Strikingly, this amount was more than 3 times greater than the costs for inpatient CAP not needing ICU admission. From a societal perspective, Kaplan et al. [48] reviewed data from Medicare and calculated that national ICU costs for CAP surpassed $2.1 billion. The financial implications of sepsis are also staggering. Multiple reports document hospital costs per case at approximately $30,000 to $40,000 [49,50]. Costs in Europe seen somewhat lower than those noted in the United States. For example, Adrie et al. [51] prospectively recorded costs for sepsis in six French ICUs. The mean cost of severe sepsis equaled € 22,800. They further described that sepsis costs varied based on whether the infection was community-acquired or evolved while the subject was hospitalized. In attempting to determine cost drivers in sepsis, Burchardi and Schneider [52] reviewed multiple costing reports and concluded that direct costs account for only 20% to 30% of overall costs in sepsis.

Cost-Effectiveness Studies in Critical Care

Coincident with the growing interest in cost-containment in critical care has been a rise in the number of formal cost-effectiveness analyses published in this field. Examples of such analyses have explored multiple resource-intense processes such as the use of MV in ARDS, reliance on renal replacement therapies (RRT) for acute renal failure in the ICU, and drotrecogin alfa (activated) (APC) for severe sepsis.

In ARDS, Hamel et al. [53] used information from the Study to Understand the Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) to investigate the value of MV. They estimated that ventilatory support was a cost-effective strategy overall, but that the cost-effectiveness ratio varied from $29,000 per QALY saved to $110,000 per QALY based on the subject's initial risk of death. Their analysis was insensitive to patient age as the cost-effectiveness ratio in subjects younger than 65 years was $32,000 versus $46,000 per QALY in those older than 75 years. One strength of this analysis was its close follow-up of patients, and thus the ability to more precisely account for postdischarge health care utilization.

Also using similar techniques, Korkeila et al. [54] investigated RRT. They tracked patients needing RRT and calculated that the costs per 6-month survivor were $80,000. In a comparable study to the one by Hamel et al., the SUPPORT investigators reported that the cost per QALY saved by initiating dialysis and continuing aggressive care was $128,000 [55]. Again, underlying prognosis, not surprisingly, affected the cost-effectiveness ratio. In the best prognosis group, cost per QALY approached $68,000. In the worse prognosis group, it measured $274,000 per QALY saved. The authors concluded that, except in those with exceedingly good prognoses, this approach was not cost-effective. Readers should note that these cost estimates are from nearly a decade ago, and if updated to reflect health care inflation would only reinforce the impression that acute RRT has substantial financial implications for society.

Finally, much emphasis has been placed on estimating the cost-effectiveness of APC because of its acquisition costs. Different groups of researchers have approached this issue from differing national perspectives (e.g., Canada vs. Europe vs. United States) [56–58]. Using data from their own ICU and results from the pivotal clinical trial for APC, Manns et al. [56] concluded that the cost per year of life gained with APC in severe sepsis was $28,000. APC was more cost-effective in persons at higher risk of death as determined by the APACHE II score ($25,000 per year of life gained). Even in older patients with more severe sepsis, APC was cost-effective. Looking at QALYs as a more traditional end point, Angus et al. [57] reached similar results. They computed that APC therapy yielded a cost of $49,000 per QALY gained. This ratio improved further if therapy was restricted to those at higher risk of death ($27,000 per QALY) [57]. Their analysis was most sensitive to the likely duration of survival with the cost-effectiveness of APC deteriorating to more than $100,000 QALY if survivors lived less than 4.6 years. Cost-effectiveness studies conducted from both UK and German perspectives have confirmed the findings of these two analyses [58,59].

Although not a definitive review of the many cost-effectiveness analyses performed in critical care outcomes research, these three examples illustrate that this approach can be used successfully to inform both professional and policy dialogue. They also help to demonstrate the value of ICU care despite its seemingly expensive implications for third-party payers and national governments. Uniformly, these reports illustrate that it is possible to measure proxies for cost rather easily and hence should become routine in the conduct of clinical research. Cost researchers, alternatively, need to be cautious as the time period they choose to study (e.g., short term, intermediate term, and long term) can affect their results and conclusions. Short-term costs may be saved with a novel intervention. Over the longer term, though, what might have appeared attractive economically could result in major costs to society.

CONCLUSION

Outcomes research remains an emerging field in critical care. As appreciation of patient-centered issues expands along with improved understanding of the diseases treated in the ICU, the need for more extensive and refined outcomes research will grow. Outcomes research, fortunately, encompasses a wide area of interest, and patient-centered outcomes can now be better folded into end points of clinical trials. Although methodologic issues continue to exist and further refinement in analytic techniques is required, the practicing intensivist needs to grasp the issues central to outcomes research.

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CHAPTER 213 ■ BIOLOGICAL AGENTS OF MASS DESTRUCTION

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OVERVIEW

The use of biological agents in warfare has been recorded throughout history. The first reported biological attack occurred in 1346 when the Tartar army used catapults to throw plague-infected corpses into the city of Kaffa. During the French and Indian War, British forces supplied blankets laden with smallpox to Native Americans supportive of the French. This caused a widespread epidemic of smallpox, leading to the surrender of Fort Carillon by Native American defenders and subsequent outbreaks of smallpox among tribes in the Ohio region [1]. In World War II, a Japanese plane reportedly dispersed rice and fleas infected with the plague organism over the city of Chu Hsien, China. An epidemic of bubonic plague developed in the Chu Hsien region shortly after this event [1].

In 1972, the United States and 161 other nations signed the Convention on the Prohibition of the Development and Stockpiling of Biological and Toxin Weapons. This international treaty prohibits the production of biological weapons and mandates the destruction of existing stockpiles. However, in 1979, there was an accidental release of aerosolized anthrax from the Institute of Microbiology and Virology at Sverdlovsk in the former Soviet Union. This resulted in an outbreak of inhalational anthrax and at least 66 deaths among the local civilian population [1].

In 1999, the Centers for Disease Control and Prevention (CDC) was designated as the lead agency in the United States for planning the public health response to a bioterrorism attack. Several reports published about that same time indicated that the risk of biological terrorism was increasing and that the use of biological agents, as both large-scale and small-scale weapons, was being actively explored by many nations and terrorist groups [2–6]. The concern expressed in these reports was realized after the attack on the World Trade Center in the fall of 2001, and when 22 cases of anthrax occurred in the United States as a result of anthrax spores being sent through the U.S. mail. There were 5 deaths among the 22 patients with anthrax [7,8]. These attacks demonstrated significant vulnerabilities of the United States to bioterrorism and the need for healthcare providers to be prepared to deal with bioterrorism attacks in their respective communities.

In 2002, the CDC published the *Public Health Assessment of Potential Biological Terrorism Agents* [9]. In this publication, potential bioterrorism agents were placed in one of three categories for the planning of public health preparedness. The agents in each category are summarized in Table 213.1. *Category A* agents have the greatest potential for the production of mass casualties and a major adverse public health impact. *Category B* agents have some potential for large-scale dissemination and mass casualties, but would be expected to cause less illness and death than Category A agents. *Category C* agents are those that do not pose a high bioterrorism threat at the present time, but could emerge as a future threat. This chapter focuses on Category A agents that have the greatest ability to cause mass casualties and significant loss of life. The Category B agent, ricin, is also discussed because of its unique potential to be used as a clandestine agent of terrorism.

SMALLPOX

The last case of endemic smallpox occurred in Somalia in 1977. In 1980, the World Health Organization (WHO) declared that the disease was eradicated. However, in recent years there has been renewed concern about the variola virus, the causative agent of smallpox, primarily due to the potential of the variola virus to be used as a biological weapon of mass destruction and the possibility for such a weapon to cause a major smallpox epidemic among infected populations. As a result of this concern, the WHO has restricted the number of laboratories officially authorized to serve as repositories for the variola virus to two: the CDC in Atlanta, Georgia, and the Vektor Institute in Novosibirsk, Russia [10].

Although smallpox has been officially declared to be eradicated, there is a possibility for its reemergence. In the nineteenth century, a major epidemic of smallpox appeared in the icy Sakha Republic in Russia, resulting in significant mortality. In the event of unusual thawing or flooding in that region, there is concern that infected corpses might be a potential source for the reemergence of smallpox. Although no live variola viruses have been isolated in the Sakha region, there is historical evidence of smallpox virus survival in interred and exhumed individuals from the eighteenth century [11].

With the increasing concern of bioterrorism and the possibility for the variola virus to be weaponized, the U.S. Military began smallpox vaccination of its troops on December 13, 2002 [12]. Much has been learned regarding the indications, contraindications, and efficacy of the vaccine since this mass immunization process began. Considerable thought has also been given to the dire consequences of a smallpox attack and the preparations necessary to manage a large-scale epidemic resulting from such an attack [13]. This section focuses on those aspects of smallpox infection that are most relevant to the critical care physician.

Virology

The causative agent of smallpox, the variola virus, is a member of the *Poxviridae* family, subfamily *Chordopoxvirinae*, and genus *Orthopoxvirus*. This genus also includes vaccinia (used in the smallpox vaccine), monkeypox virus, camelpox, and cowpox. The variola virus, like other members of the *Poxviridae* family, is a large, enveloped, DNA virus. *Poxviridae* viruses

TABLE 213.1

BIOTERRORISM AGENTS AND THREAT CATEGORIES

Category A	Category B	Category C
Bacillus anthracis (anthrax)	*Coxiella burnetii* (Q fever)	Nipah virus
Yersinia pestis (plague)	*Brucella* species (brucellosis)	Hantavirus
Variola major (smallpox)	*Burkholderia mallei* (Glanders)	Tickborne hemorrhagic fever viruses
Clostridium botulinum (botulism)	Ricin	Tickborne encephalitis viruses
Francisella tularensis (tularemia)	*Clostridium perfringens* Epsilon toxin	Yellow fever
Viral hemorrhagic fevers	Staphylococcal enterotoxin B	Multidrug-resistant tuberculosis

Adapted from Rotz LD, Khan AS, Lillibridge SR, et al: Public health assessment of potential biological terrorism agents. *Emerg Infect Dis* 8:225, 2002.

are the only viruses that can replicate in the cytoplasm of cells without involvement of the cell nucleus. The variola virus has a brick-shaped morphology, measures 260 by 150 nm, and has one of the largest viral genomes known. Its large genome makes it difficult to genetically engineer or synthesize the virus in the laboratory. Humans are the only known reservoir for the variola virus, although monkeys are susceptible to infection [14]. The variola virus is very stable and maintains infectivity for long periods of time outside the human host [15]. There are two strains of variola, variola major and variola minor. Variola major is more virulent with a mortality rate between 20% and 50% in infected individuals. Variola minor causes a similar illness, but the mortality is less than 1% [16].

Transmission and Pathogenesis

Transmission of variola occurs from person to person by respiratory droplet nuclei dispersion. Transmission is enhanced by infected individuals who have a cough. Although infrequent, infection has also been known to occur following contact with infected clothing, bedding, or other contaminated fomites [17,18].

Following inhalation, the variola virus seeds the mucus membranes of the upper and lower respiratory tract and then migrates to regional lymph nodes, where viral replication occurs. Viral replication in regional lymph nodes leads to viremia, which results in systemic dissemination of the virus to other organs including the liver, spleen, skin, lung, brain, and bone marrow, where it continues to replicate. Clinical symptoms typically develop after an incubation period of 7 to 17 days.

Clinical Manifestations

Following the initial infection period of 1 to 4 days in which viremia occurs, the clinical manifestations of smallpox appear in a series of distinct phases [18]. These phases that are uniquely characteristic of smallpox are summarized here.

Incubation Phase

The incubation phase of smallpox lasts for 7 to 17 days after infection. During this phase, the virus replicates in regional lymph nodes of the upper and lower respiratory tract. During the incubation phase, infected individuals will most likely be asymptomatic but may have minimal symptoms, such as low-grade temperature elevation or a mild, erythematous rash. Smallpox is not contagious during the incubation phase.

Prodrome Phase

Approximately 7 to 17 days after exposure and initial infection, viremia develops and the variola virus spreads systematically to mucous membranes of the oropharynx, lungs, liver, spleen, bone marrow, and dermal layer of skin. The prodrome phase is characterized by the abrupt onset of high fever (greater than 40°C), headache, nausea, vomiting, and backache. These symptoms are sometimes accompanied by abdominal pain and delirium [19]. These prodromal symptoms typically last for 2 to 4 days. Smallpox may be contagious during the prodrome phase.

Eruption Phase

The eruption phase occurs 2 to 4 days after the onset of prodromal symptoms. Enanthema of the tongue, mouth, and oropharynx precedes the eruption phase by about 1 day. The eruption phase usually begins as small, red maculopapular lesions approximately 2 to 3 mm in diameter. The lesions first appear on the face, hands, and forearms. Lower extremity lesions appear shortly thereafter. The fever usually fades as the skin lesions appear. Symptoms of the prodrome phase may continue and patients can appear very ill. During the next 2 days, the skin lesions become distinctly papular and spread centrally to the trunk. Lesions also appear on the mucous membranes of the oropharynx, and oropharyngeal sections become highly infectious. Smallpox is most contagious during the eruption phase. Healthcare workers, family members, and other close contacts are at greatest risk of contracting smallpox from an infected individual during this phase.

Vesicular Phase

In 2 to 3 days after the eruption of skin lesions, the papular lesions begin to appear vesicular. The vesicles are filled with a thick, opaque fluid and typically range from 2 to 5 mm in diameter. The vesicles are most abundant on the face and extremities. The vesicular phase usually lasts for 2 to 3 days. Humoral antibodies become detectable during this period. Smallpox is contagious during the vesicular phase.

Pustular Phase

The vesicular lesions become pustules approximately 4 to 7 days after the onset of rash. The pustules are sharply raised, firm to the touch, and may have a depressed center and become umbilicated after several days. The pustular phase lasts for 5 to 8 days. Smallpox is contagious during the pustular phase.

Crust Phase

The umbilicated pustules eventually desiccate and become crusted scabs. During this time, there may be a fever spike that may indicate the presence of a superimposed bacterial infection. The crust phase lasts for 5 to 7 days. The crusts contain virus particles and smallpox remains contagious during this phase.

Desquamation Phase

Approximately 2 weeks after the eruption of the rash, desquamation begins. During this phase, the crusts separate from the skin and begin to fall off. Crusts on the palms and soles persist the longest and typically desquamate last. Virus particles are found in the fallen-off crusts and patients are infectious until all crusts separate and fall off. The desquamation phase typically lasts for several weeks. After the crusts fall off the skin, lesions heal and form depressed, depigmented scars.

There are several important characteristics of the smallpox skin lesions that can help to distinguish smallpox from varicella infections (chickenpox). The sequential appearance of the various types of skin lesions described previously is one important characteristic. The distribution of the skin lesions is also characteristic. Smallpox lesions appear first on the face and hands, then on the upper and lower extremities and, over the course of approximately 1 week, eventually spread to the trunk. In all phases of smallpox, there is a predominance of skin lesions on the face and extremities. Another important characteristic of smallpox is that skin lesions are mostly of the same type and same stage of development throughout each clinical phase. The synchronous and centrifugal nature of the smallpox skin lesions is the hallmark of this disease. In contrast, the skin lesions associated with varicella infections are greatest on the trunk, spare the hands and soles, and are at multiple stages at any given time, with papules, vesicles, and crusts all present simultaneously [18].

The mortality rate from the usual variety of smallpox is 3% in vaccinated individuals and 30% in those who are unvaccinated [20]. Death from smallpox is presumed to be secondary to a systemic inflammatory response syndrome caused by overwhelming quantities of immune complexes and soluble variola antigen. Smallpox-associated systemic inflammatory response syndrome results in severe hypotension that usually occurs in the second week of illness. Respiratory complications, including pneumonia and bronchitis, are common [18]. Due to fever and fluid shifts during the vesicular stage of the rash, severe intravascular volume and electrolyte imbalance may occur, which can lead to the development of renal failure. Encephalitis (less than 1% affected) and bacteremia may arise, with the risk of each increasing with the severity of the disease and contributing to mortality. Osteomyelitis, arthritis, and orchitis are other rare manifestations.

There are two atypical manifestations of smallpox that have very high mortality rates [17]. Hemorrhagic smallpox occurs in less than 3% of infected individuals. The hemorrhagic form is characterized by a short incubation period and an erythematous skin eruption that later becomes petechial and hemorrhagic, similar to the lesions seen in meningococcemia. Most individuals with the hemorrhagic form of smallpox die in 5 to 6 days after onset of the rash. The malignant form, or "flat smallpox," is characterized by a fine-grained, reddish, nonpustular, and confluent rash, occasionally with hemorrhage. The malignant form occurs in 2% to 5% of infected individuals. Patients with the malignant form have severe systemic illness and most die within several days. Pulmonary edema occurs frequently in both hemorrhagic and malignant smallpox and contributes to the high mortality rates [20].

The primary long-term sequela of smallpox is the "pockmarks" that affect the skin. These are pitted lesions that permanently scar the face due to infection of sebaceous glands. Panophthalmitis, viral keratitis, and corneal ulcers can cause permanent blindness in 1% of infected individuals. Infection with smallpox results in lifelong immunity [20].

Diagnosis

The differential diagnosis of papulovesicular lesions that can be confused with smallpox includes chickenpox (varicella), shingles (varicella-zoster), disseminated herpes simplex, monkeypox, drug eruptions, generalized vaccinia, eczema vaccinatum, impetigo, bullous pemphigoid, erythema multiforme, molluscum contagiosum, and secondary syphilis. Severe chickenpox (varicella) is the most common eruption that can be confused with smallpox. Table 213.2 delineates clinical features that can help to distinguish chickenpox from smallpox.

Confirmation of smallpox can be performed by the analysis of skin scrapings, vesicular fluid, and oropharyngeal swabs. Specimens should be collected using respiratory and contact isolation procedures, ideally by previously vaccinated personnel. Specimen collection techniques and guidelines are available from public health departments, the CDC, and the WHO [18]. If smallpox is suspected, the local public health department should be notified immediately. Public health departments can provide valuable assistance in collecting specimens and getting them to an appropriate laboratory for analysis. The brick-shaped variola virus is distinguished from varicella-zoster by electron microscopy. However, polymerase chain reaction (PCR) assays are the mainstay of diagnosis at the present time. Serologic testing is not useful in differentiating the variola virus from other orthopoxviruses. Laboratory specimens

TABLE 213.2

DISTINGUISHING CLINICAL FEATURES IN SMALLPOX AND CHICKENPOX

Feature	Smallpox	Chickenpox
Prodrome	2–4 days of high fever, headache backache, vomiting, abdominal pain	Absent-to-mild, 1 day
Rash	Starts in oral mucosa, spreads to face, and expands centripetally	Starts on trunk and expands centrifugally
Palms/soles	Common	Rare
Timing	Lesions appear and progress at same time	Lesions occur in crops; lesions at varied stages of maturation
Pain	May be painful	Often pruritic
Depth	Pitting and deep scars	Superficial; does not scar

should only be manipulated and processed at laboratories with Biosafety Level 4 facilities [17]. Again, local public health departments can assist in getting specimens to an appropriate laboratory.

Infection Control

Although the primary transmission of smallpox is via respiratory droplet nuclei, infected clothing and bedding can also transmit disease [11]. Individuals with smallpox are most infectious within the first 7 to 10 days of the rash, but the disease is contagious until all crusted lesions have fallen off [17]. Secondary cases occur in family members or healthcare workers who are exposed to an infectious individual. If a new outbreak were to occur, it is anticipated that the rate of transmission may be as high as 10 new cases for every infected person. All individuals who have direct contact with the index case should be quarantined for 17 days in respiratory isolation. Home quarantine will be necessary in mass casualty situations. Healthcare workers caring for infected individuals should be vaccinated and use strict airborne and contact isolation procedures. Infected patients should be placed in respiratory isolation and managed in a negative-pressure isolation room, if possible. Patients should remain isolated until all crusted lesions have fallen off. Patients should also be vaccinated if the disease is in the early stage. If performed early, vaccination may significantly decrease the severity of smallpox symptoms [18].

Treatment

There is no U.S. Food and Drug Administration (FDA)-approved drug for the treatment of smallpox. At the present time, treatment is primarily supportive. Supportive care includes maintaining general hygiene, appropriate antibacterial therapy for secondary skin infections, daily eye irrigation for severe cases, and ensuring that the patient receives adequate nutrition and hydration. Topical treatment with idoxuridine can be considered for the treatment of corneal lesions.

Animal studies have suggested that cidofovir has activity against orthopoxviruses, including variola. Cidofovir given at the time of, or immediately following, exposure has the potential to prevent cowpox, vaccinia, and monkeypox. Aerosolized cidofovir has been shown to protect mice against intranasal challenge with the cowpox virus [21]. Additional animal studies are being conducted with other antiviral agents. A new class of potent antipoxviral drugs (ST-246 and lipid-soluble cidofovir CMX001) has been developed and stockpiled [22]. It has been demonstrated that vaccinia immune globulin decreases pulmonary viral loads and pneumonitis in animals with vaccinia or cowpox. However, there is no evidence that the use of vaccinia immune globulin offers any survival or therapeutic benefit in patients infected with smallpox.

Immunization

Smallpox eradication was possible due to a successful worldwide vaccination program with live vaccine viruses. Vaccination continues to be the mainstay of smallpox prevention. First-generation live virus vaccines (Dryvax, APSV, Lancy-Vaxina, L-IVP) were administered by puncturing the skin of the upper arm with a bifurcated needle to induce a robust humoral immunity. Many side effects, reactions, and contraindications resulted from the use of these vaccines. Second-generation vaccines produced in the last 5 to 10 years still contain replication-competent viruses produced in tissue culture and elicit an immunity level similar to first-generation vaccines. A lyophilized preparation of live vaccinia virus (Dryvax, Wyeth Laboratories, Lancaster, PA) that contains polymyxin B, streptomycin, tetracycline, and neomycin was used in the 2004–2005 U.S. vaccination program. Third-generation vaccine formulations have utilized attenuated vaccinia strains (LC16m8, MVA, NYVAC, DVVL) with the hope of an improved safety profile [23]. There has been considerable discussion regarding the efficacy of pre-exposure mass vaccination to protect the public against smallpox in the event of a bioterrorism attack. At the present time, the CDC recommends voluntary vaccination for those likely to be exposed to smallpox and "ring vaccination" in the event of a smallpox outbreak [24,25].

Within 1 week of primary vaccination, the Jennerian pustule develops a gray-white loculated pustule with central umbilication. This marks a "major reaction" and implies successful vaccination. The Jennerian pustule will then crust and darken and remain for approximately 3 weeks following immunization. Successful revaccination is marked by mild induration at the inoculation site. A repeat vaccination attempt is suggested for any equivocal responses. Due to the shortage of vaccine supply in early 2002, dilution studies showed that the vaccinia virus diluted to a titer as low as $10^{7.0}$ plaque-forming units (pfu) per mL (approximately 10,000 pfu per dose) will result in vesicle formation in 97% of inoculated individuals [26]. Dilutions to a titer of $10^{6.5}$ pfu per millimeter were only effective in 70% of those immunized. Lower doses decrease success to as low as 15% [27]. A successful primary vaccination offers full immunity for 5 to 10 years in 95% of those immunized. Successful revaccination is likely to be effective for 10 to 20 years.

The WHO and CDC instructions for the administration of smallpox vaccine are as follows [17,18,28]:

- *Site of vaccination*: Outer aspect of upper arm over the insertion of the deltoid muscle.
- *Preparation of skin*: None, unless the site is obviously dirty. Use water to cleanse the site because the use of a disinfectant can kill the virus.
- *Withdrawal of vaccine from the ampule*: A cool, sterile bifurcated needle is inserted into the reconstituted vaccine ampule. A droplet is sufficient for vaccination and is contained within the fork of the needle. Never dip the same needle back into the ampule to avoid contamination.
- *Application*: The needle is held at 90 degrees perpendicular to the skin; the needle then touches the skin to release the droplet. For primary vaccination, three strokes are made in a 5-mm area. For revaccination, 15 up/down, perpendicular strokes of the needle are rapidly made in the area of 5 mm diameter (through the drop of vaccine deposited on the skin). The strokes should be sufficiently vigorous so that a trace of blood appears at the site. If blood does not appear, the procedure (three strokes) should be repeated with the same needle.
- *Dressing*: Although the WHO does not recommend a dressing, the CDC recommends a loose sterile gauze dressing covered by a semipermeable dressing to prevent transmission of the virus. Absorb the excess blood and vaccine with gauze, and dispose the gauze in a biohazard receptacle.
- *Unused Vaccine*: Unused vaccine is good for 90 days after reconstitution and should be refrigerated without any special light precautions.

The most common adverse reactions following smallpox vaccination are tenderness and erythema at the injection site and secondary bacterial infections. Fever, malaise, local lymphadenopathy, erythema multiforme, Stevens–Johnson syndrome, urticaria, exanthems, contact dermatitis, and erythematous papules have been reported [29]. Inadvertent autoinoculation of another body site, generalized vaccinia (vesicles or pustules appearing on normal skin distant from the vaccination site), eczema vaccinatum, vaccinia keratitis, and progressive vaccinia

have been reported in primary vaccinations. Postvaccinia encephalitis is a very rare complication. Myopericarditis was reported in 200 cases from the recent military vaccination program, at a rate of 117 cases per million vaccinees [12,30]. The cause of postvaccination myopericarditis is not well understood but is probably immunologically mediated and not from direct viral infection of the myocardium. As a result, the CDC has recommended that routine vaccination should not be given to anyone with known previous cardiac disease or three or more risk factors for coronary artery disease [18,31]. The reported rate of cardiac mortality is 1.1 deaths per million primary vaccines. A review of approximately 39,000 people vaccinated against smallpox (36% primary vaccinations and 64% revaccinations) reported the following adverse reactions: encephalitis in 1 individual, myopericarditis in 21 individuals, generalized vaccinia in 2 individuals, inadvertent inoculation in 7 individuals, and ocular vaccinia in 3 individuals [32].

Contraindications to smallpox vaccination are infants less than 1 year of age, immune suppression, eczema, exfoliative skin conditions, pemphigus, cardiac disease as previously described, allergy to any component of the vaccine, and pregnant or breastfeeding women. Individuals who are taking, or have taken, high-dose corticosteroids should not be vaccinated within 1 month of completing corticosteroid therapy. Although testing for human immunodeficiency virus (HIV) is not mandatory prior to smallpox vaccination, the Advisory Committee on Immunization Practices has recommended that HIV testing be readily available to all individuals considering smallpox vaccination [25]. Individuals with a contraindication to vaccination should avoid people who have been recently vaccinated, due to possible transmission of vaccinia from viral shedding at the vaccination site. A small number of deaths (12/68) in the 1960s were attributed to unvaccinated persons exposed to recently vaccinated friends or family members [33].

Healthcare workers must be aware of the possibility for the nosocomial transmission of vaccinia during the hospitalization of a recently vaccinated patient. Nosocomial infection can result in mortality up to 11%. Direct carriage of the virus on the hands, nasal mucosa, fomites, contaminated equipment, and laundry has been implicated in the transmission of vaccinia [34]. Risk of the nosocomial transmission can be mitigated by several simple precautions. Semipermeable dressings should be applied to the site of a recent vaccination and changed frequently if there is evidence of the accumulation of purulent material. Gloves should be worn during dressing changes and meticulous handwashing with antimicrobial soap should be performed by all healthcare providers, both before and after contact with a recently vaccinated patient. Contaminated dressings should be disposed of in a biohazard container. Care should be taken to avoid contact of the vaccination site with material or equipment that could transmit the virus to other individuals. Clothing, towels, and other cloth materials that have contact with the site can be decontaminated by routine laundering with hot water. If at all possible, healthcare workers who are responsible for dressing changes should be vaccinated against smallpox, but nonvaccinated individuals are acceptable as long as appropriate precautions are observed [25]. Sexual transmission of vaccinia virus from a recently immunized active duty military member to a civilian has been recently reported following immunization [34].

Treatment of adverse effects following smallpox vaccination include supportive therapy; administration of vaccinia immune globulin; cidofovir; and an antiviral ophthalmic ointment, such as trifluridine or vidarabine, for eye involvement. Vaccinia immune globulin is available from the CDC, although the supply is limited. Cidofovir is available at no cost from the CDC under investigational use if a patient fails to respond to vaccinia immune globulin, the patient is near death, or all inventories of vaccinia immune globulin are depleted. The dose of cidofovir is 5 mg per kg, given intravenously, during 60 minutes as a single dose [18].

Due to the adverse effects of vaccinia, the federal government contracted with Acambis (Cambridge, England) and Baxter Healthcare (Cambridge, MA) to purchase a cell culture-derived smallpox vaccine that has demonstrated 94% efficacy in phase II clinical trials. Further research on the development of safer smallpox vaccines is currently in progress. In August 2007, the ACAM2000 vaccine was licensed by the FDA for administration to people at high risk of smallpox or other orthopoxvirus diseases. Over 200 million doses of the vaccine have been purchased by the U.S. Strategic National Stockpile (covers approximately 62% of the population), but it is not available for commercial use. Clinical trials show similar efficacy and side effects profile to the Dryvax vaccination, but ACAM200 cannot be diluted [18,22].

In the event of an international release of variola virus, the priority of vaccination is as follows [24,25,35]:

- *Group 1*: Individuals directly exposed to the release.
- *Group 2*: Individuals with face-to-face household contact with a directly exposed individual.
- *Group 3*: Personnel directly involved in the evaluation, care, or transport of infected patients.
- *Group 4*: Laboratory personnel responsible for handling and processing specimens, and others who may be exposed to infectious materials.

ANTHRAX

In the fall of 2001, 22 cases of anthrax with 5 deaths occurred in the United States as a result of anthrax spores in envelopes sent through the U.S. mail. Early recognition and treatment of anthrax by astute clinicians was responsible for preventing additional deaths [7,8]. Anthrax is thought to be the most likely biological agent to be used in a bioterrorism attack. Identification of a single case should prompt notification of local, state, and national public health authorities [36]. The CDC has rapid response teams with specialized expertise, training, and equipment that can be deployed immediately to assist local authorities in the event of a bioterrorism attack [8]. Cases of anthrax in animals have been reported to occur sporadically in North America. In 2006, an outbreak was reported in Canada that affected over 900 animals. Two cases of cutaneous anthrax and one case of inhalational anthrax in humans were reported in the United States from occupational exposure associated with drum making using animal hides from West Africa [37].

Microbiology

Bacillus anthracis (from the Greek word for coal, *anthrakis*) is a large, Gram-positive, aerobic, spore-forming, nonmotile bacillus. *B. anthracis* is found in the soil of many regions of the world, where it exists in the endospore form. Its virulence is determined by two plasmids. One plasmid involves the synthesis of a poly-D-glutamic acid capsule that inhibits phagocytosis of vegetative bacilli and the other contains genes for the synthesis of exotoxins. The exotoxins are known as *protective antigen, edema factor*, and *lethal factor*. The *protective antigen* is a binding protein that is necessary for entry into the host cell and combines with both edema factor and lethal factor to produce "edema toxin" and "lethal toxin" [38]. Edema toxin converts adenosine triphosphate to cyclic adenosine monophosphate (cAMP), resulting in high intracellular cAMP levels that impair water homeostasis and thereby cause cellular edema. Lethal toxin stimulates the overproduction of cytokines, primarily tumor necrosis factor-α and interleukin-1-β that cause

macrophage lysis. The sudden release of inflammatory mediators appears to be responsible for the marked clinical toxicity of the bacteremic form of anthrax.

Clinical Manifestations

There are three forms of anthrax infection. The clinical characteristics of each form are determined by the route of entry of the anthrax spores. *Cutaneous anthrax* is the most common naturally occurring form, comprising approximately 95% of cases reported. Spores enter the body through breaks in the skin and begin low-level germination within days, resulting in soft tissue or mucosal edema and localized necrosis. Initially, a painless, pruritic macule appears, followed by vesiculation, ulceration, and a black, "coal-like" painless eschar, from which anthrax gets its name. The eschar sloughs within 2 to 3 weeks of onset [39]. Abscess formation occurs only with superinfection. Endospores phagocytosed by macrophages are often transported to regional lymph nodes causing painful lymphadenopathy and lymphangitis. Infrequently, cutaneous anthrax may spread hematogenously with significant morbidity and death in a small number of individuals. Cutaneous anthrax has been reported to cause microangiopathic hemolytic anemia, renal dysfunction, and coagulopathy [40].

Gastrointestinal and *oropharyngeal anthrax* usually occur following the ingestion of contaminated meat. This is a rare manifestation of anthrax, with most cases occurring in Africa. Mucosal ulcers, edema, and regional lymphadenopathy are initial manifestations. In the oropharyngeal form, pseudomembranes are seen in the oropharynx and upper airway obstruction can develop. In the gastrointestinal form, a necrotizing infection progresses from the esophagus to the cecum. Fever, nausea, vomiting, abdominal pain, gastrointestinal bleeding, and bloody diarrhea are typical symptoms. Anemia, electrolyte abnormalities, and hypovolemic shock may follow. Massive ascites that is occasionally purulent has been reported. Death results from intestinal perforation or septicemia [20].

The third form of anthrax infection is *inhalational anthrax*. Anthrax spores are 1 to 1.5 μm in size and easily deposit in the alveoli following inhalation. There, the endospores are phagocytosed by the pulmonary macrophages and transported via lymphatics to the mediastinal lymph nodes, where they may remain dormant as "vegetative cells" for approximately 10 to 60 days or longer. Once germination in the lymph nodes is complete, bacterial replication occurs. The replicating bacteria release edema and lethal toxins that produce a hemorrhagic mediastinitis.

In some patients, the initial symptoms are relatively mild and nonspecific, resembling an upper respiratory tract infection. Fever, chills, fatigue, nonproductive cough, nausea, dyspnea, chest pain, and myalgias are common presenting complaints (Table 213.3) [36,37]. These symptoms typically last for 2 to 3 days and then progress to a more severe, fulminant illness. However, some patients present with fulminant illness without any prodromal symptoms. Dyspnea and shock characterize the fulminant phase of inhalational anthrax. The number of spores inhaled, age of the patient, and the underlying immune status most likely affect the clinical course of the disease [41]. Chest radiographs show mediastinal widening and pleural effusions that may be massive (Fig. 213.1). *B. anthracis* bacilli, bacillary fragments, and anthrax antigens can be identified by immunohistochemistry testing of the pleural fluid [42]. Although parenchymal infiltrates are not prominent, a focal hemorrhagic necrotizing pneumonitis, resembling the Ghon complex of tuberculosis, was noted in 11 of 42 autopsy patients from the accidental release of anthrax in Sverdlovsk, USSR, in 1979. Almost 50% of patients with inhalational anthrax develop hemorrhagic meningitis as a result of the hematogenous spread of *B. anthracis*. Massive bacteremia, with up to 10^7 to 10^8 bacteria per mL of blood, causes overwhelming septic shock and death within hours after the onset of symptoms. According to the Defense Intelligence Agency, the lethal dose to kill 50% of persons exposed (LD_{50}) to weapons-grade anthrax is 2,500 to 55,000 spores [43]. However, as few as one to three spores may be sufficient to cause infection [36].

TABLE 213.3

CLINICAL FEATURES OF INHALATIONAL ANTHRAX (U.S. OUTBREAK 2001, n = 10)

Feature	Incidence (%)
Fever and chills	100
Fatigue, malaise, lethargy	100
Cough	90
Nausea/vomiting	90
Dyspnea	80
Sweats-drenching	70
Chest discomfort	70
Myalgias	50
Headache	50
Confusion	40
Abdominal pain	30
Sore throat	20
Rhinorrhea	10

Adapted from Inglesby TV, O'Toole T, Henderson DA, et al: Anthrax as a biological weapon. *JAMA* 287:2236, 2002.

Diagnosis

A high index of suspicion is necessary to make the diagnosis of anthrax when patients present with a severe flulike illnesses. Laboratory findings from the U.S. outbreak in 2001 showed that patients had a mild neutrophil-predominant leukocytosis,

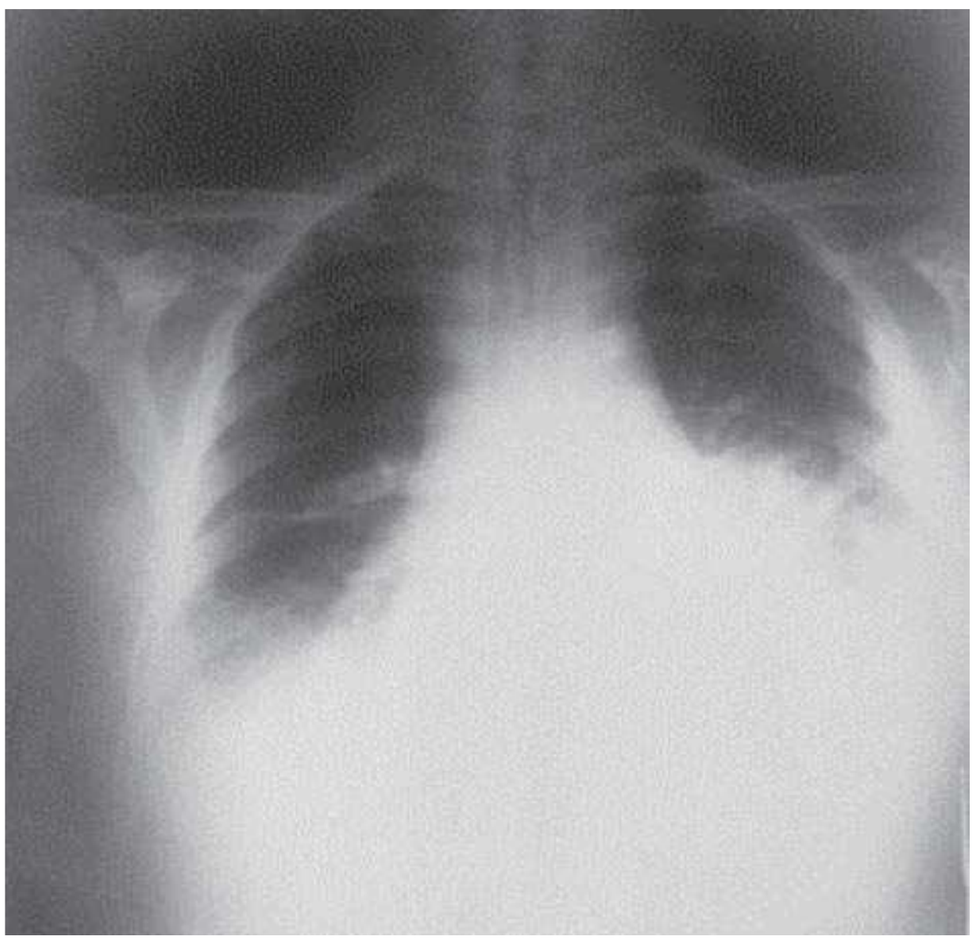

FIGURE 213.1. Chest radiograph from a patient with anthrax showing mediastinal widening and a pleural effusion. [From the CDC Web site: http://www.bt.cdc.gov/agent/anthrax/anthrax-images/inhalational.asp.]

in the range of 7,500 to 13,300 per µL. Peak white blood cell count during illness ranged from 11,900 to 49,600 per mm^3. Elevated transaminases, hyponatremia, and hypoxemia were also noted [7,37,41,43]. One hundred percent of these patients had an abnormal chest radiograph with mediastinal widening, pleural effusions, consolidation, and infiltrates predominating. The presence of mediastinal widening that may require computed tomography scanning to elucidate should be considered diagnostic of anthrax until proven otherwise [44–46]. Hemorrhagic necrotizing lymphadenitis and mediastinitis are pathognomonic of anthrax, but these are autopsy findings of these conditions [19]. *B. anthracis* is easily cultured from blood, cerebral spinal fluid, ascites, and vesicular fluid with standard microbiology techniques. The laboratory should be notified when the diagnosis of anthrax is being considered, as many hospital laboratories will not further characterize *Bacillus* species unless requested. Biosafety Level 2 conditions apply for workers handling specimens because most clinical specimens have spores in the vegetative state that are not easily transmitted [36]. The presence of large Gram-positive rods in short chains that are positive on India ink staining is considered presumptive of *B. anthracis*, until the results of cultures and other confirmatory tests are obtained. Confirmatory testing can be performed by the CDC Laboratory Response Network. Rapid detection tests based on immunohistochemistry, and PCR techniques are available via the Laboratory Response Network [37]. Nasal swabs are not recommended because they are not reliable for making the diagnosis of anthrax. Following the 2001 anthrax attack, there were negative nasal swab results in patients with fatal inhalational anthrax [43]. In June 2004, the FDA approved the Anthrax Quick ELISA test (Immunetics, Inc., Boston, MA) that detects antibodies to the protective antigen of *B. anthracis* exotoxin. The test can be completed in less than 1 hour and is available to hospital and commercial laboratories by the manufacturer [37].

Treatment

Due to the fulminant course of inhalational anthrax, prompt initiation of therapy is essential for survival. Ciprofloxacin (400 mg) or doxycycline (100 mg) given intravenously every 12 hours with one to two other antibiotics that have predicted efficacy against anthrax is currently recommended. Additional antibiotics that are effective against anthrax include rifampin, vancomycin, imipenem, chloramphenicol, penicillin, ampicillin, clindamycin, and clarithromycin. Two survivors of anthrax during the U.S. outbreak received parenteral ciprofloxacin, clindamycin, and rifampin. The addition of clindamycin may attenuate toxin production [44]. There are limited data regarding treatment of pregnant women for anthrax. However, the limited information that is available suggests that the use of ciprofloxacin during pregnancy is unlikely to be associated with a high risk for structural birth defects [47]. Therefore, ciprofloxacin should be given to pregnant women for the treatment of inhalational anthrax unless otherwise contraindicated. Doxycycline is relatively contraindicated in pregnancy and should only be considered if ciprofloxacin is unavailable or absolutely contraindicated. Therapy with ciprofloxacin or doxycycline should continue for 60 days. Patients can be switched to oral therapy with ciprofloxacin (500 mg twice daily) or doxycycline (100 mg twice daily) after fulminant symptoms have resolved and they are stable. The use of systemic corticosteroids has been suggested for meningitis, severe edema, and airway compromise. Parenteral ciprofloxacin and another antibiotic with good central nervous system penetration, such as rifampin, should be part of the initial treatment regimen for anthrax meningitis. Cutaneous anthrax with systemic involvement, significant edema, and lesions of the head and neck should be treated similarly. Uncomplicated cutaneous anthrax can be treated with oral ciprofloxacin or doxycycline for 7 to 10 days, but, due to the possibility of concomitant inhalational exposure, a 60-day course is recommended [36,37].

A review of anthrax cases in adults from 1900 to 2004 noted that fulminant inhalational anthrax is often fatal despite advances in medical care. Early diagnosis and initiation of therapy during the prodromal phase improved survival and are pivotal for decreasing mortality in inhalational anthrax [48]. Similarly, a review of anthrax cases in children from 1900 to 2005 shows that early diagnosis and treatment of all forms of anthrax are critical for improved survival in children [49].

Prophylaxis

All patients exposed to anthrax should receive prophylaxis with oral ciprofloxacin (500 mg twice daily), levofloxacin (500 mg daily), or doxycycline (100 mg twice daily) for 60 days, regardless of laboratory test results. Nasal swabs can confirm exposure to anthrax, but cannot exclude it. High-dose penicillin or ampicillin may be an acceptable alternative for 60 days in patients who are allergic or intolerant to the recommended antibiotics [36,37]. More than 5,000 people received postexposure prophylaxis following the 2001 U.S. outbreak, but only about half completed the 60-day course. The main reasons for discontinuing therapy were gastrointestinal or neurologic side effects (75%) or a low perceived risk (25%).

The anthrax vaccine (AVA-Biothrax) manufactured by BioPort Corporation in Lansing, Michigan, is the only licensed human anthrax vaccine in the United States. The vaccine consists of supernatant material from cultures of a toxigenic, nonencapsulated strain of *B. anthracis*. A six-dose series has been used by the U.S. Military. The anthrax vaccine is not available to the general public at the present time. Although efficacy data are limited to goat hair mill workers from the 1950s to 1974, fully vaccinated individuals did not contract anthrax as compared to those who did not participate in the vaccine program [50]. Approximately 95% of vaccinated individuals seroconvert after the third dose of vaccine. Data regarding vaccine safety from more than 1 million doses administered to members of the U.S. Military reveal that the adverse events were without any significant pattern or association. The vaccine is generally considered to be safe by the FDA [50]. A review by the U.S. Army Medical Research Institute of Infectious Diseases reported a 1% (101/10,722) incidence of systemic symptoms, most commonly headache. Local or injection site reactions occurred in 3.6% [36]. A study comparing four subcutaneous injections of anthrax vaccine adsorbed (AVA) with three and four intramuscular injections of AVA showed similar immunoprotection at 7 months with less adverse effects at the injection site. Following an aerosolized *B. anthracis* attack, postexposure prophylactic vaccination and antibiotic therapy remain the most effective and least expensive strategies [51].

TULAREMIA

Tularemia is a zoonosis found in a wide range of animals, primarily small mammals such as rodents and rabbits. In 1922, tularemia was reported to cause fatal illness in humans [52]. In the late 1920s, tularemia was recognized as a threat to laboratory workers. Tularemia is caused by *Francisella tularensis*, an intracellular, nonspore-forming, aerobic Gram-negative coccobacillus. In the mid-twentieth century, both the United States and the former Soviet Union developed biological weapons that could disperse *F. tularensis* [53]. Biological weapons have now been banned and are no longer in production. However, there is concern that *F. tularensis* could be used as an agent

of bioterrorism. In a 1970 report, the WHO estimated that 50 kg of aerosolized *F. tularensis* dispersed over a metropolitan area of 5 million people could cause 19,000 deaths and 250,000 incapacitating illnesses [19,54]. The impact of such an attack would probably linger for several weeks to months due to disease relapses [54].

Microbiology

F. tularensis is a nonsporulating, nonmotile, Gram-negative coccobacillus. It is a hardy organism, which makes it well suited for use as an agent of bioterrorism. It can survive in moist soil, water, and animal carcasses for many weeks. However, chlorination of water prevents its spread through water contamination. *F. tularensis* can be aerosolized and inhalation of aerosolized organisms poses a threat to those exposed. The most common isolate, and the most virulent form, is *F. tularensis* biovar *tularensis* (Group A). Inoculation or inhalation of as few as 10 organisms may cause clinical disease [55–57]. *F. tularensis* biovar *palaearctica* is found mostly outside of the United States, most notably in Europe. Transmission of *F. tularensis* to humans occurs predominantly through tick and fleabites, handling of infected animals, ingestion of contaminated food and water, and inhalation of the aerosolized organism. There is no human-to-human transmission of *F. tularensis*. As a biological weapon, the organism would most likely be dispersed as an aerosol and cause mass casualties from an acute febrile illness that may progress to severe pneumonia [19].

Epidemiology

Tularemia occurs worldwide but is rare in Africa, Central, South America, and the United Kingdom, with highest incidence in Russia and Scandinavian countries [57–59]. In the United States, tularemia cases are reported most often from the south central and western states (Arkansas, Illinois, Missouri, Oklahoma, Tennessee, Texas, Utah, Virginia, and Wyoming). The predominant mode of transmission to humans in the United States is by tick bites, and most cases are reported in spring and summer. Hunters and trappers exposed to animal reservoirs are at high risk for exposure [57–59]. In Europe and Japan, mosquito bites and the handling of infected animals appear to cause the disease. A large outbreak of tularemia in 2003 along with small summer outbreaks between 1995 and 2005 in Sweden suggests environmental sources clustering around recreational areas [60]. Tularemia epidemics may have a seasonal presentation. *F. tularensis* var *tularensis*, often seen in summer, is tick-borne, while *F. palaearctica*, seen in fall and winter, is commonly transmitted from contaminated water, rodents, or aquatic animals. An outbreak of tularemia in Martha's Vineyard, Massachusetts, during the summer of 2000 was associated with lawn mowing and brush cutting [61,62]. A waterborne outbreak resulting in 21 cases of oropharyngeal and 5 cases of glandular tularemia was reported in Georgia [63].

Pathogenesis

F. tularensis enters the human host via the eye, respiratory tract, gastrointestinal tract, or a break in the skin. The virulence of the organism depends on its ability to replicate within the macrophage. On entering the macrophage, the organism proliferates. This is followed by apoptosis of the macrophage and the release of a larger number of organisms, leading to involvement of the local lymph nodes and bacteremia. Once bacteremia develops, *F. tularensis* infects the lungs, pleura, spleen, liver, and kidney. The host defense against *F. tularensis* is reported to be T-cell independent in the first 3 days and T-cell dependent after 3 days of infection. Initially, a focal suppurative necrosis with polymorphonuclear cells, macrophages, epithelioid cells, and lymphocytes are noted. The predominant protective mechanism in containing the disease comes from cell-mediated immunity. On histopathology, granulomas with necrosis may be seen in infected organs. Following inhalational exposure, hemorrhagic airway inflammation progressing to bronchopneumonia, pleuritis, and pleural effusion have been reported [55–57]. The mucosal immunopathogenesis of *F. tularensis* in animal models has shown that the antibodies may provide both prophylactic and therapeutic protection against pulmonary infection when there is active cell-mediated immunity [64].

Clinical Features

The clinical manifestations of tularemia depend on the site of entry, exposure dose, virulence of the organism, and host immune factors. Hematogenous spread may occur from any of the initial clinical presentations. Tularemia can have various clinical presentations that have been classified as primary pneumonic, typhoidal, ulceroglandular, oculoglandular, oropharyngeal, and septic. The *ulceroglandular form* is the most common naturally occurring form of tularemia. After an incubation period of 3 to 6 days (range, 1 to 25 days) following a vector bite or animal contact, patients present with symptoms of high fevers (85%), chills (52%), headache (45%), cough (38%), and myalgias (31%). They may also have malaise, chest pain, abdominal pain, nausea, vomiting, and diarrhea. A pulse-temperature dissociation is often seen. At the site of inoculation, a tender papule develops that later becomes a pustule and ulcerates. Lymph nodes draining the inoculation site become enlarged and painful (85%). Infected lymph nodes may become suppurative, ulcerate, and remain enlarged for a long period of time. Exudative pharyngitis and tonsillitis may develop following ingestion of contaminated food or inhalation of the aerosolized organism. Pharyngeal ulceration and regional lymphadenopathy may be present. A systemic disease caused by *F. tularensis* without lymph node enlargement and presenting with fever, diarrhea, dehydration, hypotension, and meningismus is referred to as the *typhoidal form*. The *pneumonic form* of tularemia may occur as a primary pleuropneumonia following the inhalation of aerosolized organisms. The pneumonic form may also occur as a result of hematogenous spread from other sites of infection or following oropharyngeal tularemia. After an inhalational exposure, constitutional symptoms, such as fever and chills, typically precede the onset of respiratory symptoms. The respiratory symptoms include a dry or minimally productive cough, pleuritic chest pain, shortness of breath, and hemoptysis. Pleural effusions, either unilateral or bilateral, can occur. Pneumonic tularemia can rapidly progress to respiratory failure with acute respiratory distress syndrome, multiorgan failure, disseminated intravascular coagulation, rhabdomyolysis, renal failure, and hepatitis [55–57,65]. Rarely, peritonitis, pericarditis, appendicitis, osteomyelitis, erythema nodosum, and meningitis have been reported to occur in tularemia. It has been reported that delays in diagnosis and failure to institute prompt aminoglycoside therapy results in higher morbidity [66]. The mortality rate of untreated tularemic pneumonia is 60%, but with proper antibiotic therapy the mortality rate is significantly reduced to 1% to 2.5% [55,56].

Laboratory and Radiographic Findings

A high index of suspicion is needed in order to make an early diagnosis of tularemia. Lack of response to conventional treatment for skin ulcers or community-acquired pneumonia, along

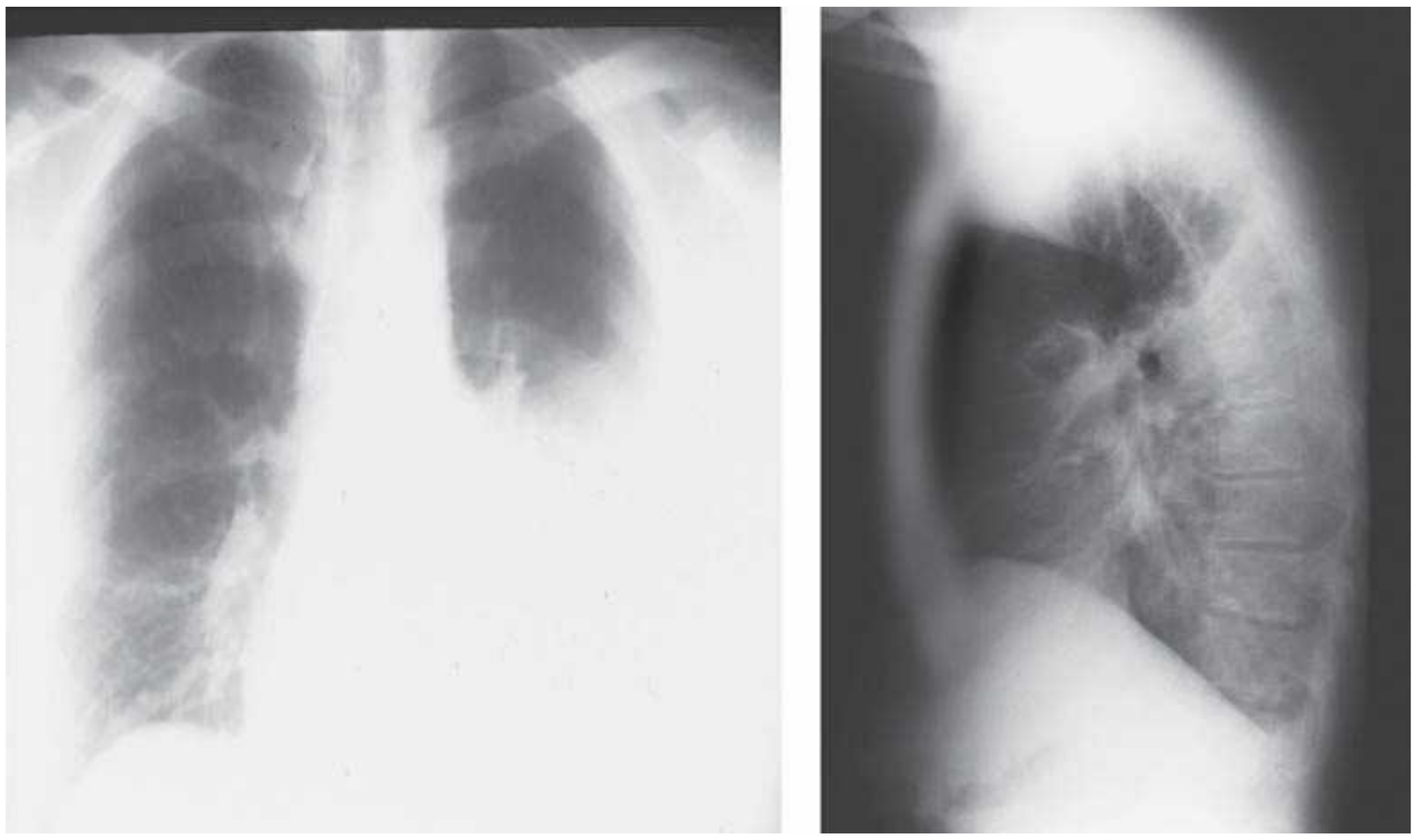

FIGURE 213.2. Chest radiograph from a 27-year-old man who contracted tularemic pneumonia after skinning a rabbit that he had hunted. [Courtesy of Angeline A. Lazarus, MD.]

with a history of exposure to animals, may alert the clinician to think of tularemia. Routine laboratory tests, such as a complete blood count and serum chemistry panels, are generally nondiagnostic. A complete blood count may show a leukocytosis with a normal differential or mild lymphocytosis. Mild elevations of lactic dehydrogenase, transaminases, and alkaline phosphatase may be seen on a serum chemistry panel. If rhabdomyolysis is present, an elevated serum creatine kinase concentration and urine myoglobin may be seen. Sterile pyuria has been reported. Mild abnormalities in cerebrospinal fluid cell counts, protein, and glucose have also been reported [54,56,65].

Tularemia can present with multiple abnormalities on a chest radiograph (Fig. 213.2). A report of the chest radiographic findings in 50 patients who had a confirmed diagnosis of tularemia showed the following abnormalities: patchy airspace opacities (74%, unilateral in 54%); hilar adenopathy (32%, unilateral in 22%); pleural effusion (30%, unilateral in 20%); unilateral lobar or segmental opacities (18%); cavitation (16%); oval opacities (8%); and cardiomegaly with a pulmonary edema pattern (6%). Rare findings such as apical infiltrates, empyema with bronchopleural fistula, miliary pattern, residual cyst, and residual calcification occurring in less than 5% of patients were also reported [67].

Diagnosis

It is possible to isolate *F. tularensis* from sputum, blood, and other body fluids, but the organism can be difficult to culture. Culture media must contain cysteine or sulfhydryl compounds for *F. tularensis* to grow. Notification of laboratory personnel that tularemia is suspected can be helpful in enhancing the yield of culture. Notification of laboratory personnel will also help to ensure that they observe appropriate biosafety procedures when manipulating specimens. Routine diagnostic procedures can be performed in Biosafety Level 2 conditions. Examination of cultures in which *F. tularensis* is suspected should be done in a biological safety cabinet. Manipulation of cultures and other procedures that might produce aerosols or droplets should be conducted under Biosafety Level 3 conditions [56].

Examination of secretions and biopsy specimens with direct fluorescent antibody or immunochemical stains may help to identify the organism. The diagnosis is often made through serologic testing using enzyme-linked immunosorbent assay (ELISA). Serologic titers may not be elevated early in the course of disease. A fourfold rise is typically seen during the course of illness. A single tularemia antibody titer of 1:160 or greater is supportive of the diagnosis [55,56,65]. The combined use of ELISA and confirmatory Western blot analysis was found to be the most suitable approach to the serological diagnosis of tularemia [67,68]. Other diagnostic methods include antigen detection assays and PCR [68–70]. A multitarget real-time TaqMan PCR assay (Applied Biosystems, Foster City, CA) has been reported to have high sensitivity and specificity for the diagnosis of tularemia and may be a valuable tool for the analysis of clinical specimens and field samples following a bioterrorism attack [71].

Treatment

The antibiotic of choice for the treatment of tularemia is streptomycin, 1 g, given intramuscularly (IM) twice daily. Gentamicin, 5 mg per kg, given IM or intravenously (IV) once daily, can be used instead of streptomycin. For children, the preferred antibiotics are streptomycin, 15 mg per kg, given IM twice daily (not to exceed 2 g per day) or gentamicin, 2.5 mg per kg, given IM or IV thrice daily. Alternate choices for adults are doxycycline, 100 mg, given IV twice daily; chloramphenicol, 15 mg per kg, given IV four times daily; or ciprofloxacin, 400 mg, given IV twice daily. For children, alternate choices are doxycycline, 100 mg, given IV twice daily if the child weighs 45 kg or more, and doxycycline, 2.2 mg per kg, given IV twice daily for children weighing less than 45 kg. Chloramphenicol and ciprofloxacin can also be used as alternate antibiotics in children. The ciprofloxacin dose in children should not exceed 1 g per day. Gentamicin is preferred over streptomycin for treatment during pregnancy. Chloramphenicol should not be given to pregnant patients. Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days. Treatment with doxycycline or chloramphenicol should be continued for 14 to 21 days. Patients beginning treatment with

doxycycline, chloramphenicol, or ciprofloxacin can be switched to oral antibiotics when clinically appropriate. β-Lactams and macrolides are not recommended for treatment of tularemia [56,72].

In a mass casualty setting caused by tularemia, the preferred antibiotic for adults and pregnant women is doxycycline, 100 mg, taken orally twice daily, or ciprofloxacin 500 mg, taken orally twice daily. For children, the preferred choices are doxycycline, 100 mg, taken orally twice daily if the child weighs 45 kg or more; doxycycline, 2.2 mg per kg, taken orally twice daily if the child weighs less than 45 kg; or ciprofloxacin, 15 mg per kg, taken orally twice daily and not to exceed 1 g per day. It is recommended that therapy be continued for 3 to 14 days. In immunosuppressed patients, either streptomycin or gentamicin is the preferred antibiotic in mass casualty situations [56,57].

Prophylaxis

Individuals exposed to *F. tularensis* may be protected against systemic infection if they receive prophylactic antibiotics during the incubation period. For postexposure prophylaxis, either doxycycline, 100 mg, taken orally twice daily, or ciprofloxacin, 500 mg, taken orally twice daily for 14 days, is recommended. Both doxycycline and ciprofloxacin can be taken by pregnant women for postexposure prophylaxis, but ciprofloxacin is preferred. Postexposure prophylaxis for children is the same as treatment during mass casualty situations [56,57].

Immunization

In Russia, a live attenuated vaccine has been used to offer protection to those living in tularemia-endemic areas. In the United States, a live attenuated vaccine has been given to laboratory personnel working with *F. tularensis*. The currently available vaccine does not offer total protection against inhalational exposure to *F. tularensis*. Therefore, vaccination is not recommended for postexposure prophylaxis. The intranasal administration of an attenuated live vaccine has been shown to provide protection against intranasal infection with *F. tularensis* biovar A in mice. The use of such a vaccine in humans requires further investigation [55,56,73,74].

PLAGUE

Plague is a zoonotic infection, primarily seen in rodents and rabbits. Humans are infected as an accidental host. Historically, three pandemics with bubonic plague occurred in the sixth, fourteenth, and nineteenth centuries, killing millions of people in Europe, Africa, and Central and Southern Asia. The fourteenth century pandemic became known as the "Black Death." This pandemic reportedly took the lives of more than 40 million people [75]. In recent years, the highly contagious nature of plague has raised concern about its possible use as an agent of bioterrorism.

Microbiology

Plague is caused by *Yersinia pestis*, a Gram-negative, nonmotile coccobacillus of the family *Enterobacteriaceae*. *Yersinia pestis* has a bipolar staining pattern with Wright–Giemsa or Wayson stain that gives a "safety pin" appearance to the stained organism (Fig. 213.3). From recent genetic studies of *Yersinia pestis*, it appears that there are three biovars and that the original organism has undergone chromosomal rearrangements over the years, leading to new ribotypes of the biovars. Three plasmids of *Yersinia pestis* have been identified as the source of virulence factors. Virulence factors include plasminogen activator, lipopolysaccharide endotoxin, V antigen, F1 antigen, and W antigen. These virulence factors confer antiphagocytic activity, cytotoxicity, and facilitate use of host nutrients to escape other host defense mechanisms [76–81]. The lipopolysaccharide endotoxin is responsible for the systemic inflammatory response, acute respiratory distress syndrome, and multiorgan failure [77,82].

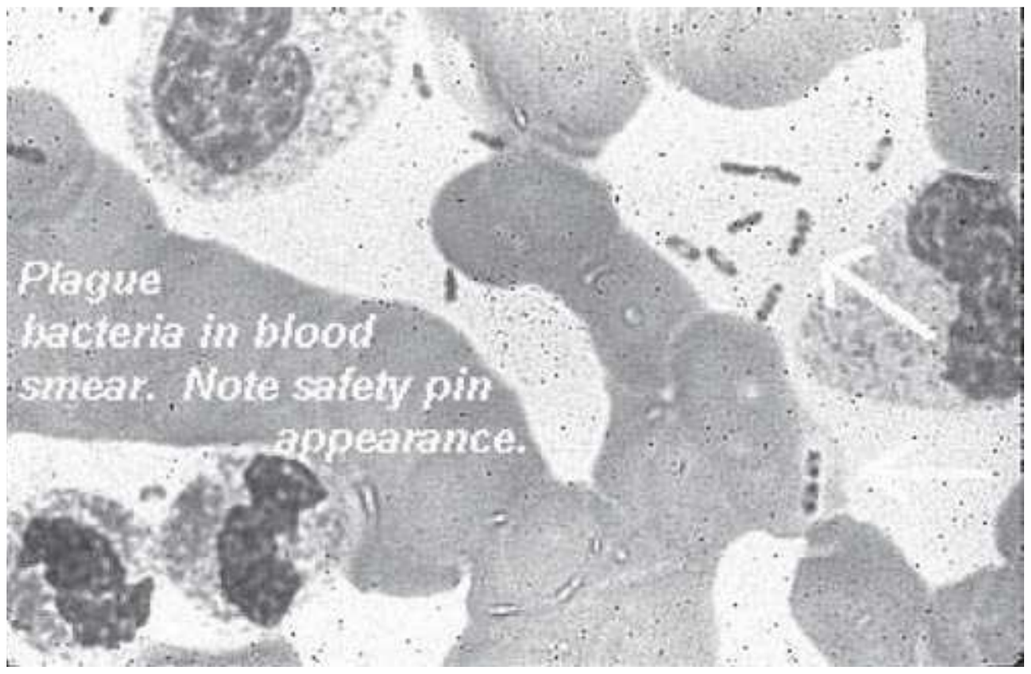

FIGURE 213.3. Wright–Giemsa stain of *Yersinia pestis* showing the characteristic bipolar staining pattern that gives a "safety pin" appearance to the organism. [From the CDC Web site: http://www.cdc.gov/ncidod/dvbid/plague/p1.htm.]

Plague is naturally transmitted by the bite of a plague-infected flea. Rodents, particularly rats and squirrels, are the natural reservoirs that transmit *Yersinia pestis* to fleas. After ingestion of blood from an infected animal, bacteria multiply in the digestive tract of the flea. Hundreds of bacteria are then regurgitated into the next animal or human victim of the plague-infected flea. Plague can be transmitted by all species of fleas; protection against fleabites is an important preventive measure in endemic areas and during epidemics. In the United States, the most common vector for the transmission of plague to humans is the *Diamanus montanus* flea. The most important reservoirs in the United States include ground squirrels, rock squirrels, and the prairie dog. Transmission to humans also occurs by direct contact with infected live or dead animals, inhalation of respiratory droplets from patients with pneumonic plague, or from direct contact with infected body fluids or tissue [76–78,82,83].

Plague as a Bioweapon

The use of plague as an intentional agent of warfare first occurred in 1346 with the Tartars catapulting the plague-infected corpses of their troops to the Christian Genoese troops during the siege of Kaffa. Since that time, plague has been used by the military forces of Russia against Sweden, and Japan against China. The biowarfare program of United States had plague in its arsenal before destroying biological weapons in the early 1970s. The CDC has classified plague as a Category A threat agent. Aerosolized droplets of *Yersinia pestis* could be used as a biowarfare agent, resulting in the highly fatal pneumonic form of plague [76,77,84]. Plague is contagious from person to person and can result in a greater number of casualties than those initially exposed and infected. The WHO estimates that 50 kg of *Yersinia pestis* aerosolized over a population of 5 million people may result in 150,000 infections and 36,000 deaths [53]. Intentional dispersion of *Yersinia pestis* as an aerosol will lead to pneumonic plague, while the release of infected fleas will usually result in bubonic or septicemic plague [53,76,77,84].

Epidemiology

Plague has been reported worldwide, with most human cases occurring in the developing countries of Africa and Asia. The WHO reports global occurrence of 1,000 to 3,000 cases per year. More than 90% of plague cases reported in the United States come from the states of Arizona, New Mexico, California, and Colorado, with rare cases from Texas. The majority of cases occur in spring and summer, when people come in contact with rodents and fleas while outdoors. In endemic areas of the United States, there is a higher incidence of plague among Native Americans compared to non-Native Americans [76,77,85–88]. In Uganda, 127 clinical cases of plague (88% bubonic, 12% pneumonic) were identified in 2006. Of these, 28 patients (22%) died and 11 of these had pneumonic plague. In one family, four members died of pneumonic plague [89]. Two small outbreaks of oropharyngeal plague were reported from the Middle East from the eating of raw camel liver and meat [90,91]. The WHO reported an outbreak of plague in the Democratic Republic of the Congo, consisting of 130 cases of pneumonic plague, 61 of which were fatal [92]. Smaller outbreaks of plague continue to occur throughout the world [93]. Recent studies have suggested that the Black Death pandemic probably led to mutations in the chemokine receptor CCR5. These mutations may confer immunity to certain individuals against plague and other infections, such as HIV-1 [94].

Pathogenesis

The common forms of naturally acquired human plague are *bubonic, septicemic*, and *primary pneumonic* forms. The bubonic and septicemic forms are the most common presentations. After entering the body through a fleabite, bacteria migrate via cutaneous lymphatics to the regional lymph nodes and are subjected to phagocytosis. If not killed by host defense systems, the bacteria proliferate within the macrophages with the aid of fraction I, an envelope antigen of *Yersinia pestis*. Other virulence factors secreted by the bacteria facilitate extracellular spread and resistance to destruction. The initial infection in lymph nodes causes lymphadenitis and local swelling that is referred to as the "bubo"; hence, the name "bubonic plague." Most buboes develop in the groin, axilla, or neck. Virulence factors perpetuate the progression of disease, leading to septicemia and the infection of other organs. Endotoxins released by *Yersinia pestis* result in the septic state and increased resistance to host defenses [76–82].

Inhalation of infected droplets of *Yersinia pestis* results in primary pneumonic plague. The primary pneumonic form is rapid in onset with an incubation period of 1 to 6 days (mean, 2 to 4 days). Presenting features are fevers, chills, cough, and blood-tinged sputum. Following inhalation into the lungs, *Yersinia pestis* organisms are engulfed by macrophages and transported to the lymphatic system and regional lymph nodes. This is followed by transient bacteremia that results in the seeding of other organs such as the spleen, liver, skin, and mucous membranes. Secondary pneumonic plague occurs as sequelae of bubonic or primary septicemic plague. Primary septicemic plague occurs when there is direct entry of *Yersinia pestis* bacilli into the bloodstream. The early recognition of primary septicemic plague is difficult because it resembles other febrile illnesses with septicemia. Other rare forms of plague are *plague meningitis* and *plague pharyngitis*. Plague meningitis occurs following the hematogenous spread of *Yersinia pestis* bacilli to the meninges. Plague pharyngitis may occur following the ingestion or inhalation of *Yersinia pestis* bacilli. Both plague meningitis and plague pharyngitis cause cervical lymphadenitis [76,78].

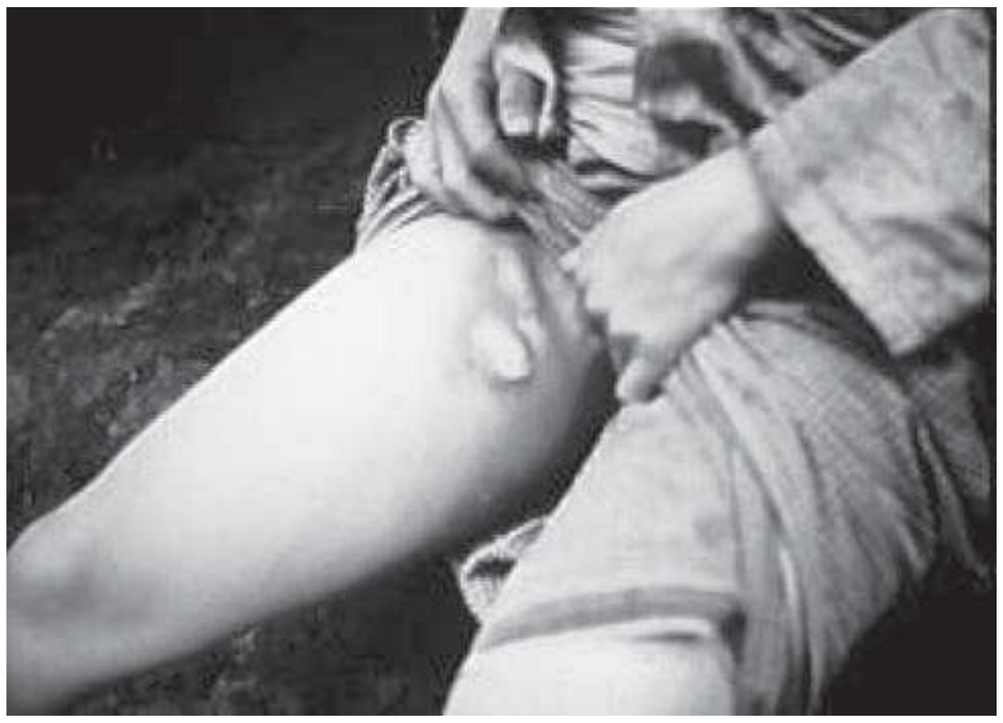

FIGURE 213.4. Bubonic plague with the characteristic bubo. [From CDC Web site: http://www.cdc.gov/ncidod/dvbid/plague/diagnosis.]

Clinical Presentation

The incubation period and clinical manifestations of plague vary according to mode of transmission. Of the plague cases seen in the United States, 85% are bubonic plague, 10% to 15% are primary septicemic plague, and less than 1% are primary pneumonic plague. Bubonic plague may progress to septicemic or pneumonic plague in 23% and 9% of cases, respectively. The clinical presentation of plague in children is similar to that of adults. There are little data regarding unique manifestations of plague in pregnant women [76,77,82,89,95,96].

Bubonic Plague

Following the bite of an infected flea, fever, chills, and headache will develop in 1 to 8 days. Nausea, vomiting, malaise, altered mentation, cough, abdominal pain, and chest pain may also be present. Patients then develop lymphadenitis, buboes (Fig. 213.4), and severe pain. Based on site of inoculation, palpable, regional buboes appear in the groin, axillae, or cervical regions, with erythema of the overlying skin. These enlarged lymph nodes are necrotic and contain dense concentrations of *Yersinia pestis* bacilli [76,77,95].

Septicemic Plague

A minority of patients exposed to *Yersinia pestis* develop septicemic plague, either as a primary form (without buboes) or secondary to the hematogenous spread of bubonic or primary pneumonic plague. The clinical features are similar to those of Gram-negative sepsis, with fever, chills, nausea, vomiting, and hypotension. Abdominal pain from hepatosplenomegaly, acral cyanosis, disseminated intravascular coagulation, and purpura has been reported. Severe anxiety and confusion may occur. Endotoxin released from *Yersinia pestis* may produce severe hypotension, oliguria, anuria, and acute respiratory distress syndrome. Gangrenous changes of the fingers, toes, and nose may occur. As a result of these manifestations, septicemic plague has been called the Black Death. Without treatment, the mortality rate of septicemic plague is 100% [75–77,87–89].

Pneumonic Plague

Primary pneumonic plague occurs by inhaling respiratory droplets from infected humans or animals and is characterized

by a severe, rapidly progressive pneumonia with septicemic features that is rapidly fatal if not treated within 24 hours. Plague is highly contagious by the airborne route. Following an incubation period of 1 to 6 days, there is a rapid onset of fever, dyspnea, chest pain, and cough that may be productive of bloody, watery, or purulent sputum. Tachycardia, cyanosis, nausea, vomiting, diarrhea, and abdominal pain may occur. Intra-alveolar edema and congestion are commonly seen. Buboes are generally absent, but may develop in the cervical area. Acute respiratory failure requiring mechanical ventilation may occur. Strict respiratory isolation should be observed because pneumonic plague is highly contagious [76,77,97–99]. Chest radiographs show bilateral alveolar opacities (89%) and pleural effusions (55%). Cavitations may occur [98]. Alveolar opacities in secondary pneumonic plague may have a nodular appearance. Mediastinal adenopathy is very rare in primary pneumonic plague but hilar node enlargement is often present. This can help to distinguish primary pneumonic plague from anthrax if bioterrorism is suspected and a causative agent has not been identified [100,101]. Without prompt treatment, the mortality rate of primary pneumonic plague is 100% [75].

Secondary pneumonic plague occurs in approximately 12% of individuals with bubonic plague or primary septicemic plague. It develops as a result of the hematogenous spread of *Yersinia pestis* bacilli to the lungs. It typically presents as a severe bronchopneumonia. Common symptoms include cough, dyspnea, chest pain, and hemoptysis. Chest radiographs typically show bilateral, patchy alveolar infiltrates that may progress to consolidation. In contrast to primary pneumonic plague, mediastinal, cervical, and hilar adenopathy may occur [76,100,101]. A chest radiograph from a patient with secondary pneumonic plague is shown in Figure 213.5.

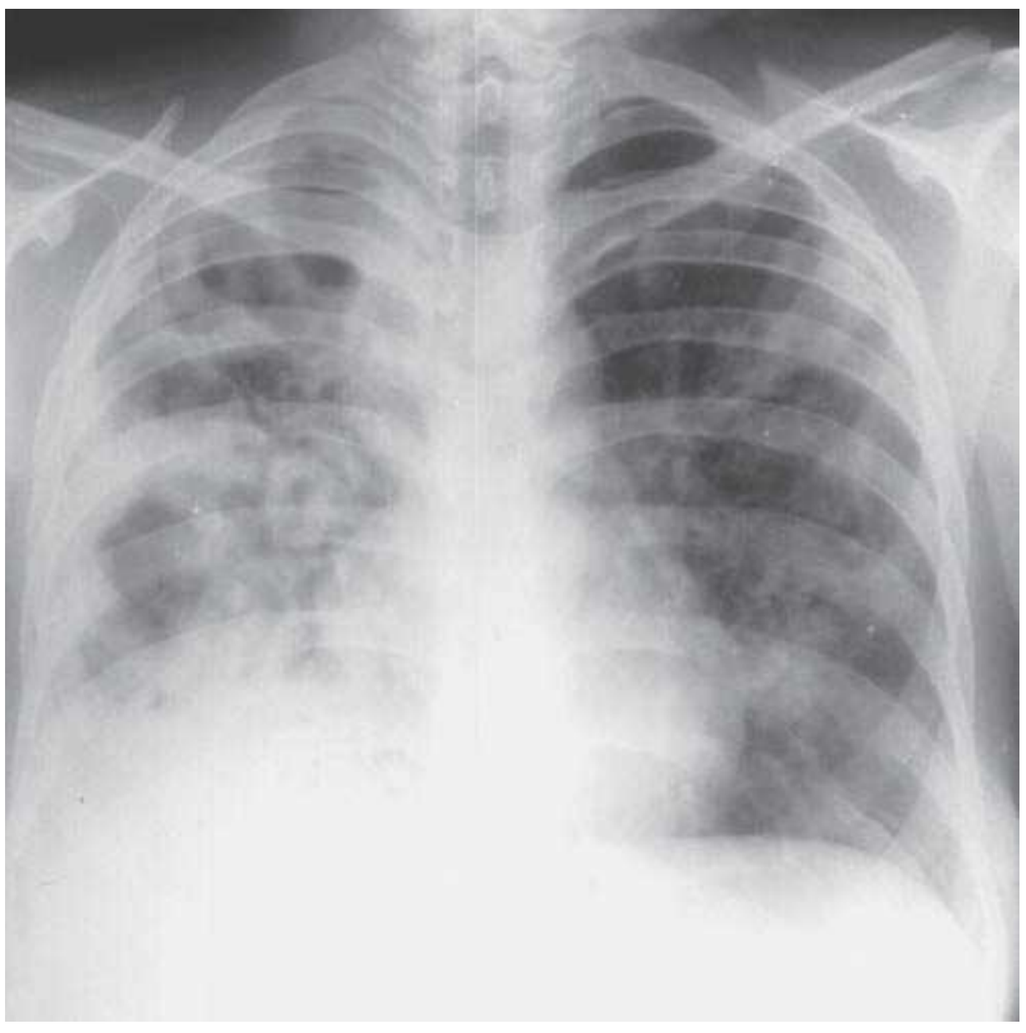

FIGURE 213.5. A 38-year-old man from Himachal Pradesh was admitted with complaints of fever, cough, hemoptysis, and dyspnea. There is endemicity of pneumonic plague where the patient came from due to the prevalent custom of hunting wild rats and rodents. Sputum examination was positive for *Yersinia pestis*. The patient was successfully treated with antibiotics. [Chest radiograph courtesy of Sanjay Jain, MD, Department of Internal Medicine, and Surinder K. Jindal, MD, Professor of Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.]

Diagnosis

The diagnosis of septicemic and pneumonic plague is challenging when buboes are not present. A high index of suspicion is critical in making an early diagnosis so that appropriate therapy can be started as soon as possible. The presence of Gram-negative rods in bloody sputum of an immunocompetent host should suggest pneumonic plague. In the event of multiple, simultaneous cases of rapidly progressive pneumonia, pneumonic plague should be considered in the differential diagnosis. For suspected bubonic plague, the differential diagnosis includes tularemia, cat scratch disease, suppurative adenitis, scrub typhus, tuberculosis, chancroid, and lymphogranuloma venereum [76,77].

Laboratory Diagnosis

A mild-to-moderate leukocytosis with neutrophil predominance and toxic granulations are seen in all forms of plague. In severe cases, elevated transaminases, azotemia, and coagulopathy with disseminated intravascular coagulation are often seen. The sputum is usually purulent, often blood-tinged, and contains *Yersinia pestis* bacilli. A Gram's stain of sputum, blood, or lymph node aspirate may show Gram-negative coccobacilli. Identification of the organism may be difficult by Gram's stain alone because an improperly decolorized specimen can cause *Yersinia pestis* to resemble a Gram-positive diplococcus as a result of its bipolarity. Microscopic examination of a sputum specimen prepared with Wright–Giemsa stain will show the characteristic bipolar staining pattern more clearly (Fig. 213.3). Cultures may be positive for *Yersinia pestis* within 24 to 48 hours. Misidentification of *Yersinia pestis* may occur with automated bacterial identification devices [76,77]. Rapid diagnostic tests such as immunoglobulin-M immunoassay, direct fluorescent antibody testing, and PCR are available in certain laboratories. Direct fluorescent antibody staining for *Yersinia pestis* (Fig. 213.6) and dipstick antigen detection tests are highly specific and are available at some centers [76,77,102–105]. A rapid diagnostic test using monoclonal antibodies to the F1 antigen has recently been field-tested in Madagascar and was shown to be comparable in specificity and sensitivity to detection by ELISA in both bubonic and pneumonic plague. This rapid diagnostic test shows promise for the early on-site diagnosis of

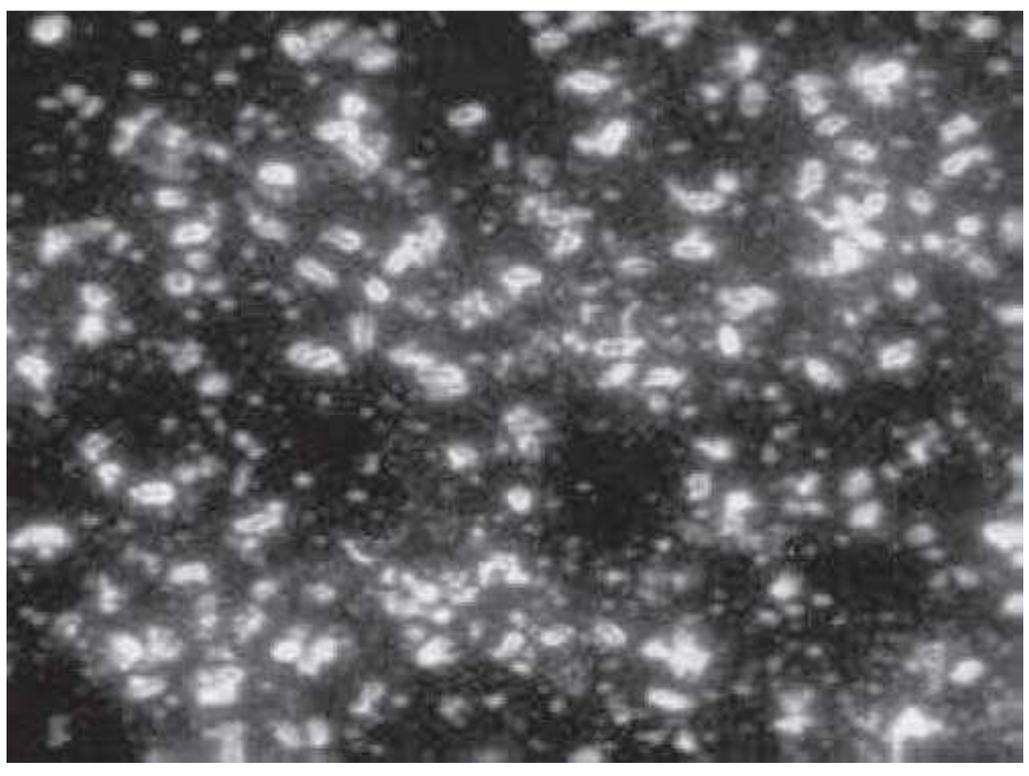

FIGURE 213.6. Fluorescence antibody positivity for *Yersinia pestis* is seen as bright, intense green staining around the bacterial cell. [From CDC Web site: http://www.cdc.gov/ncidod/dvbid/plague/bacterium.htm.]

plague [103]. Additional tests for detection and confirmation that are available through the Laboratory Response Network include PCR assays, molecular-based subtyping, and immunohistochemistry on formalin-fixed tissues [77].

The CDC recommends that plague should be suspected in persons with symptoms of fever and lymphadenopathy if they reside in, or have recently traveled to, a plague-endemic area and if Gram-negative and/or bipolar-staining coccobacilli are seen on a smear taken from affected tissues or other specimens. The diagnosis of plague should be presumed if immunofluorescence staining of smear or material is positive for the presence of *Yersinia pestis* F1 antigen and/or a single serum specimen shows the anti-F1 antigen in a titer of greater than 1:10 by agglutination. In order to confirm the diagnosis of plague, the CDC recommends that one or more of the following criteria be met: isolation of *Yersinia pestis* from a clinical specimen, a single *Yersinia pestis* antibody titer of more than 1:128 dilution, or a fourfold rise in paired sera antibody titer to *Yersinia pestis* F1 antigen. Antibody susceptibility testing should be done at a reference laboratory because there are no standardized procedures for such testing [76,77,105]. Plague as a bioterrorism agent should be suspected when multiple cases of severe and rapidly progressive pneumonic plague cases are seen with fulminant systemic symptoms and hemoptysis.

Treatment

Traditionally, streptomycin or gentamicin has been the mainstay of therapy for *Yersinia pestis*. Other acceptable antibiotics are ciprofloxacin, tetracycline, doxycycline, and chloramphenicol [75–77,82,83,106–109]. The recommendations of the Working Group on Civilian Biodefense for treatment of adult patients with plague in a small, contained casualty setting is streptomycin 1 g IM, given twice daily; gentamicin, 5 mg per kg IM or IV, once daily; or a 2 mg per kg loading dose of gentamicin followed by 1.7 mg per kg IM or IV thrice daily. The dosing of aminoglycosides must include adjustment for renal function. Alternate choices include doxycycline, 100 mg IV, given twice daily or 200 mg IV given once daily; ciprofloxacin, 400 mg IV, given twice daily; or chloramphenicol, 25 mg per kg IV, given four times daily. For pregnant women with plague, the treatment of choice is adult dosing with gentamicin, as described previously. Alternative choices for pregnant women include ciprofloxacin or doxycycline with dosing similar to that of other adults. It should be noted that doxycycline is relatively contraindicated in pregnancy and should only be given to pregnant women if other antibiotics are unavailable or contraindicate. For children, the preferred antibiotics are streptomycin, 15 mg per kg IM, given twice daily (maximum dose of 2 g per day), or gentamicin, 2.5 mg per kg IM or IV, given thrice daily. Alternate antibiotics for children include doxycycline at the adult dose if the child weighs more than 45 kg; doxycycline, 2.2 mg per kg IV, given twice daily if the child weighs under 45 kg; ciprofloxacin, 15 mg per kg IV, given twice daily; or chloramphenicol, 25 mg per kg IV, given four times daily. The duration of treatment is 10 days. For breastfeeding mothers and infants, treatment with gentamicin is recommended. Alternate therapy with fluoroquinolones can be used in either setting. The treatment of immunosuppressed individuals is similar to that of immunocompetent individuals [76,77].

Mass Casualty Treatment and Prophylaxis

In a mass casualty situation from the intentional release of plague, the urgency to initiate prompt treatment of infected individuals, as well as prophylaxis for those exposed but uninfected, may cause a significant stress on healthcare capabilities. The ability to administer parenteral streptomycin or gentamicin will be limited. The Working Group on Civilian Biodefense recommends the use of ciprofloxacin, 500 mg, taken orally twice daily or doxycycline, 100 mg, taken orally twice daily for adults and pregnant women, both for treatment and postexposure prophylaxis. The alternate choice is chloramphenicol, 25 mg per kg, taken orally four times daily. For children, the preferred choices are the adult dose of doxycycline if the child weighs more than 45 kg and 2.2 mg per kg orally twice daily for child weighing less than 45 kg. Children may also be given ciprofloxacin, 20 mg per kg, orally twice daily, or chloramphenicol, 25 mg per kg, orally four times daily. For breastfeeding mothers and infants, treatment with doxycycline is recommended. The duration of treatment is 7 days. All individuals who come within 2 m of a patient with pneumonic plague should receive postexposure prophylaxis. These recommendations are consensus-based for treating plague following an intentional release or bioterrorism attack and may not reflect the FDA-approved use or indications [76,77].

Immunization

Vaccination with a killed, whole-cell vaccine against plague was available in the United States until 1999 for those at high risk for exposure, such as military personnel, those working in endemic areas, and laboratory personnel working with *Yersinia pestis*. The vaccine was not effective against pneumonic plague, and adequate protection in a biowarfare setting is doubtful. Several studies of newer vaccines against plague are ongoing. Vaccines using F1 capsular antigen of doxycycline, 100 mg, taken orally twice daily *pestis* and monoclonal antibodies specific to the F1 and V antigens have shown promising results against pneumonic plague in animal models. Phase I studies with recombinant F1 and V antigens are underway. However, there is no approved vaccine for use against plague available in the United States at the present time [77,110–112].

Infection Control

Patients suspected of plague should be isolated and antibiotic therapy should be instituted promptly. Universal exposure precautions, respiratory isolation using CDC droplet precautions, and special handling of blood and discharge from buboes must be followed. In cases of pneumonic plague, strictly enforced respiratory isolation in addition to the use of masks, gloves, gowns, and eye protection must be continued for the first few days of antibiotic therapy. Following 2 to 4 days of therapy with appropriate antibiotics, patients with both nonpneumonic plague and pneumonic plague may be removed from isolation [113–115]. Laboratory workers should be warned of potential plague infection because cases of laboratory-acquired plague have been reported [98].

Preventive Measures

For naturally occurring cases, the primary preventive measure for plague is rodent and flea control. In endemic areas, the use of insect repellant, the wearing of gloves while handling wild animals, and avoiding rodent burrows will reduce exposure to *Yersinia pestis* [113,114].

BOTULINUM TOXIN

Botulinum is an extremely potent toxin produced by *Clostridium botulinum*, an anaerobic, spore-forming bacterium that is present in the soil. Unlike botulinum toxin that is inactivated by

temperatures above 85°C for 5 minutes, *Clostridium* spores can survive temperatures of 105°C for up to 4 hours, but are readily destroyed by chlorine. Spores may remain viable for over 30 years in a dry state and are resistant to ultraviolet light exposure [116,117]. The botulinum toxin produced by *Clostridium botulinum* is the most poisonous substance known. It can cause a serious, life-threatening paralytic illness in exposed individuals, is easily produced in a laboratory, and can be easily transported. In view of these properties, botulinum toxin has been identified as a major bioterrorism threat [116,118]. It has been designated as a Category A bioterrorism threat by the CDC [10]. There are reports that several countries may have stockpiled or are developing botulinum toxin for use as a bioweapon [116,118]. The general features and management of botulism are presented in Chapters 88 and 175, but the implications of botulism as a bioterrorist weapon are discussed here.

Botulinum Toxin as an Agent of Bioterrorism

There are three forms of naturally occurring botulism: *Foodborne botulism, wound botulism*, and *intestinal (infant and adult) botulism*. All forms of botulism can produce a serious paralytic illness that can lead to respiratory failure and death.

Botulinum toxin solution is a colorless, odorless, tasteless liquid that is easily inactivated by heating at a temperature greater than 85°C for 5 minutes. There are seven different antigenic types that are named botulinum A, B, C, D, E, F, and G. Given its extreme potency, botulinum toxin can produce devastating effects and mass casualties if intentionally dispersed by aerosol or used to contaminate the water supply. One gram of botulinum toxin has the capacity to kill more than 1 million persons if aerosolized [117,118]. Botulinum toxin types A, B, E, and F have been associated with naturally occurring foodborne botulism. Types C and D botulinum toxin cause natural disease in birds and cattle. Type G botulinum toxin is found in South America, but it has not been associated with foodborne botulism. Inhalational challenge studies with aerosolized botulinum toxin in monkeys have demonstrated the development of illness following exposure to types C, D, and G. Researchers suspect that humans are also susceptible to these types [118–120].

The intentional use of botulinum toxin can be either inhalational or foodborne. In the 1930s, the Japanese reportedly executed a number of Manchurian prisoners by feeding them cultures of *Clostridium botulinum*. During World War II, there was concern that Germany had weaponized botulinum toxin for use as a biowarfare agent. This led to the production of more than 1 million doses of botulinum toxoid vaccine for allied forces in Europe, but the vaccine was never given. Botulinum toxin was produced by the United States for use as a bioweapon from World War II to the early 1970s when the bioweapon program was terminated. Following the 1972 Convention on the Prohibition of the Development and Stockpiling of Biological and Toxin Weapons, both the former Soviet Union and Iraq continued to develop botulinum toxin as a biowarfare agent. After the 1991 Persian Gulf War, Iraq admitted to U.N. weapons inspectors that it had produced and stockpiled biological weapons containing botulinum toxin. It has been reported that several countries may continue to produce or stockpile botulinum toxin for use as a bioweapon [118].

At the present time, there is considerable concern about the potential use of botulinum toxin as an agent of bioterrorism. Contamination of either a food or a beverage source that can retain the potency of botulinum toxin can result in mass casualties, serious illness among affected individuals, the overwhelming of hospitals, enormous stress on intensive care units, and significant anxiety among the general population [117,118]. It has been estimated that 1 g of botulinum toxin added to milk that is commercially distributed and consumed by 568,000 individuals can result in 100,000 cases of botulism [121]. It has also been estimated that 1 g of aerosolized botulinum toxin could potentially kill more than 1 million people [118]. The dispersion of aerosolized botulinum toxin in the unsuccessful terrorist attacks in Japan during the early 1990s suggests that botulinum toxin could be used in future bioterrorism attacks.

Pathogenesis

Following exposure by inhalation or ingestion, the toxin is activated, enters the circulation, and the heavy chain of the toxin gets bound to the neuronal membrane on the presynaptic side of the neuromuscular junction. The toxin then enters the neuronal cell, after which the light chain of the toxin cleaves the synaptic proteins that form the synaptic fusion complex. Disruption of the synaptic fusion complex prevents release of acetylcholine release into the synaptic cleft. Without acetylcholine, the affected muscle becomes paralyzed. Muscle paralysis can last for several months. Death from botulism is caused by failure of the respiratory muscles to contract. The central nervous system is unaffected as botulism toxin does not cross the blood–brain barrier. A prospective, observational cohort study of 91 botulism patients in Thailand showed that those individuals presenting with dyspnea, moderate-to-severe ptosis, and papillary changes were likely to progress to respiratory failure, while a long incubation period before symptoms appeared was associated with a more favorable prognosis [122].

Treatment

The treatment of botulism includes supportive care, mechanical ventilation if necessary, and the administration of botulinum antitoxin. In an outbreak following an intentional release, the healthcare demands may overwhelm current capabilities, especially with regard to the availability of mechanical ventilators and critical care providers. At present, there is an ongoing U.S. government effort to stockpile mechanical ventilators that can be deployed in the event of a mass casualty.

Rega et al. suggest an algorithm to assess the severity of botulism cases that may be helpful in mass casualty situations [123]. Specific therapy for botulism involves the administration of botulinum antitoxin. Early suspicion of botulism and the prompt administration of botulinum antitoxin can reduce nerve damage and disease severity. However, any muscle paralysis existing prior to antitoxin administration will not be reversed. The goal of antitoxin therapy is to prevent further paralysis by neutralizing unbound botulinum toxin in the circulation. If the type of botulinum toxin is known, a type-specific antitoxin can be given. If the toxin type is not known, the trivalent antitoxin containing neutralizing antibodies against botulinum toxin types A, B, and E should be given. Botulinum antitoxin is available from the CDC through state and local health departments. If another type of toxin is intentionally dispersed during a bioterrorism attack, consideration may be given for the use of an investigational heptavalent antitoxin (ABCDEFG) that is in the possession of the U.S. Army. Physicians should review the package insert prior to administering the antitoxin to familiarize themselves with the dose, dilution, and mode of administration. A new heptavalent botulinum antitoxin (HBAT) approved by the FDA replaced the former botulinum antitoxin in 2010. This heptavalent antitoxin contains equine-derived antibody to all the seven botulinum toxins from A to G. If a case of botulism is suspected, prompt diagnosis is

essential. If botulism is confirmed, the CDC will provide the new heptavalent antitoxin and detailed instructions for its intravenous administration [124]. Additional doses of botulinum antitoxin will be needed if multiple cases of botulism occur after an intentional release. Following the initial administration of botulinum antitoxin, patients should be carefully assessed for refractory problems, such as rapidly progressing paralysis, severe airway obstruction, or overwhelming respiratory tract secretions, which may indicate the need for an additional dose. Hypersensitivity reactions to botulinum antitoxin may occur. These include anaphylaxis, serum sickness, chills, fever, dyspnea, cutaneous erythema, and edema of the tongue. The incidence of hypersensitivity with the recommended one-vial dose is about 1%. A small dose can be given initially to screen for hypersensitivity, but this would be impractical in a mass casualty situation [116–118,125–127].

Prophylaxis

In the United States, a pentavalent botulinum toxoid is available from the CDC for the immunization of laboratory workers who may be exposed to botulinum toxin and for the protection of military personnel in the event of a biowarfare attack. It may be obtained on an investigational basis for others at high risk for botulinum toxin exposure. Botulinum toxoid, 0.5 mL, is given subcutaneously at 0, 2, and 12 weeks, followed by a booster dose at 1 year. Adequate immunity against botulinum toxin is assessed by measuring antitoxin titers. In one study, an adequate response was noted in 91% of those immunized against toxin A and 78% of those immunized against toxin B. In an animal study, the intranasal administration of botulinum toxin in mice, with and without prechallenge immunization with pentavalent toxoid, showed intra-alveolar hemorrhage and interstitial edema in both groups, but the immunized mice were protected from lethality and nervous system changes in comparison to nonimmunized mice [128].

Mass immunization of the public with botulinum toxoid is not recommended and is not currently available. It takes several months to attain acquired immunity following the administration of botulinum toxoid and, therefore, it is not effective for postexposure prophylaxis. Recent evidence suggests that a recombinant oligoclonal antibody may have efficacy in preventing and treating botulism. Animal studies have shown promise for using the heavy chain of the botulinum toxin molecule as an inhalational agent for the treatment of botulism [116–118,125,128].

RICIN

Ricin is a potent toxin that belongs to the broad family of ribosome-inhibiting proteins and is easily extracted from seeds contained in the bean of the castor plant, *Ricinis communis*. "Ricinus" is the Latin word for tick and the plant was given this name for the resemblance of castor bean seeds to engorged ticks [129]. The castor plant, a native plant of Africa, is a common outdoor plant in warm climates and is also used for ornamental purposes. Castor bean seeds, castor oil, and the castor plant itself have been used for many centuries for their medicinal (laxative and purgative), lubricant, and decorative properties. Castor bean seeds contain high concentrations of ricin. Ingestion of as few as three seeds can be fatal. Ricin is an immunotoxin, allergen, and toxic enzyme that inhibits protein synthesis. As a result of its biochemical properties, ricin has antitumor effects and has undergone phase I and phase II clinical trials as a chemotherapeutic agent. Ricin can be inactivated by heating to 175°F for 10 minutes. It can be produced in liquid, crystalline, or dry powder forms. Both the liquid and powder forms have the potential to be aerosolized [130,131].

Toxicology

Ricin is an enzyme consisting of two sulfide-linked polypeptide chains, A and B. The A-chain enters the cytosol of a cell, inactivates the 28S ribosomal subunits, inhibits protein synthesis, and causes cell death. The B-chain binds to the cell surface at galactose-containing sites and facilitates entry of the A-chain into the cell [132,133]. Most of the data regarding the toxicity of ricin come from animal experiments. Both the toxicity and the lethality of ricin depend on the exposure dose and the route of administration. In experiments using mice, the LD_{50} and time of death are 3 to 5 µg per kg and 60 hours by inhalation, 5 µg per kg and 90 hours by intravenous injection, and 20 mg per kg and 85 hours by intragastric administration. The lethal doses of ricin in humans have been calculated to be approximately 5 to 10 µg per kg by inhalation and 1 to 10 µg per kg by injection [134–137]. On exposure to lethal doses of ricin by inhalation, rats develop a necrotizing tracheobronchitis and pneumonia with parenchymal inflammation and pulmonary edema. These pathologic changes lead to alveolar flooding and hypoxemia. Immunohistochemical stains show that ricin binds to bronchiolar cells, macrophages, and alveolar lining cells. In nonhuman primates, inhalation of ricin leads to death within 48 hours of exposure, and autopsy shows diffuse necrosis of airways, severe pulmonary edema, severe fibrinopurulent pneumonia, and mediastinal lymphadenitis [135]. Animal data show that the Kupffer cells are the primary targets of ricin-induced injury to the liver [134]. Ricin toxicity is not contagious to other individuals.

Ricin as an Agent of Bioterrorism

The high toxicity, relative ease of production, ease of dissemination, and stability of ricin in ambient conditions make it a potential agent of bioterrorism. Ricin can be dispersed as an aerosol or as a contaminant of food and beverages for the purpose of causing multiple casualties. Most experts agree that it would be logistically difficult to use ricin for the production of large-scale mass casualties because it would take a very large amount to do so [138]. However, ricin may be an ideal agent for small-scale bioterrorism attacks against high-value targets. Dozens of people could be killed in such attacks and the psychological impact on a community could be enormous.

There have been several reports of the use or intended use of ricin in terrorist activities. In 1978, a Bulgarian diplomat, Georgi Markov, was killed in London by a ricin-containing pellet fired from an umbrella-based weapon [139,140]. In January 2003, British authorities arrested 10 individuals from North Africa who were residing in a London apartment where ricin was found [140]. In October 2003, ricin was identified in an envelope at a Greenville, South Carolina, post office [140–142]. In November 2003, an envelope addressed to the White House was reportedly intercepted by the Secret Service and was found to contain ricin [140]. In February 2004, ricin was reportedly detected in the Dirksen Senate Office Building [140]. These events highlight the need for critical care providers to be familiar with the recognition and management of ricin poisoning.

Ricin Toxicity in Humans

The pathologic changes and clinical symptoms caused by ricin exposure depend on the exposure dose and the route of

exposure. The clinical effects of ricin in humans have been described following cases of castor seed ingestion and parenteral use in chemotherapeutic clinical trials. There are limited clinical data regarding ricin toxicity via inhalational route in humans. The clinical findings observed in animal models after the oral or parenteral administration of ricin appear to correlate with the clinical findings of humans exposed to oral or parenteral ricin. Therefore, the findings from animals following inhalational exposure are presumed to be similar to those that would be experienced by humans following ricin inhalation. Leukocytosis appears to be a constant finding, regardless of the route of exposure. Ricin toxicity by any route of exposure can produce hallucinations and seizures.

Gastrointestinal Route

The ingestion of castor seeds can cause human illness that ranges from mild to severe, based on the amount of ricin ingested. Compared to other routes of ricin exposure, the gastrointestinal route is the least toxic. A review of 751 cases of castor seed ingestion reported symptoms consisting of nausea, vomiting, and abdominal cramping within a few hours after ingestion, followed by diarrhea that may become bloody and lead to both dehydration and volume depletion. Patients developed hypotension, severe fluid and electrolyte loss, tachypnea, tachycardia, and sweating. There were case fatality rates of 8.1% for untreated individuals and 0.4% for treated individuals. Death occurred approximately 72 hours after exposure. In addition, sore throat, dilation of the pupils, altered mental status, hallucinations, and seizures were noted in some patients. On autopsy, hepatic necrosis, renal necrosis, necrosis of the gastrointestinal mucosa with local hemorrhage, and mesenteric lymph node necrosis were found. The hepatic and renal damage may be secondary to vascular collapse rather than the result of direct toxin injury [131,143–146].

Parenteral Route

In cases of ricin toxicity produced by parenteral administration, pain at the site of injection, fatigue, malaise, headache, rigors, and fever were noted in the first 24 hours. Patients also showed local necrotic lymphadenopathy. Ricin, when used as a chemotherapeutic agent at a dose of 18 to 20 µg per kg, caused nausea, vomiting, myalgia, and fatigue [131]. More serious adverse effects may include pulmonary edema, hypoalbuminemia, cardiac failure, hypotension, hypovolemic shock, acute hepatorenal failure, gastrointestinal bleeding, thrombocytopenia, and bleeding diathesis [131–133,143,147–149].

Inhalational Route

Patients with inhalational exposure of ricin may develop symptoms within 3 to 24 hours. The only information regarding human exposure to the inhalational form comes from exposure to castor seed dust. Reported symptoms from dust inhalation include itchy eyes, nasal and bronchial congestion, urticaria, chest tightness, and wheezing. Severe bronchospasm has been reported [131]. In an accidental exposure, ricin caused fever, chest tightness, dyspnea, cough, nausea, and arthralgias in 4 to 8 hours. These symptoms are suggestive of an allergic syndrome. Based on animal data following high-dose inhalational exposures, one may expect humans to develop cough, dyspnea, chest pain, cardiac dysfunction, cyanosis, arthralgias, airway necrosis, alveolitis, high permeability pulmonary edema, adult respiratory distress syndrome, and acute respiratory failure. The mortality rate in animals is high following ricin inhalation and usually occurs within 36 to 72 hours. It appears that ricin causes endothelial cell damage with fluid and protein leak with edema [131–133,143].

Ricin as an Allergen

Allergic responses of types I and IV have been reported following dermal exposure to castor seeds and castor seed dust. A case report describes an anaphylactic-type reaction in a woman when one of the seeds from her castor-bean necklace disintegrated in her fingers. The woman experienced rhinitis, sneezing, periorbital edema, and facial urticaria requiring a subcutaneous injection of epinephrine [150–152]. Urticaria has been reported following the inhalation of castor seed dust [150]. Although the incidence of ricin-associated allergic reactions is unknown, they may be relatively frequent among exposed individuals because of the immunogenic properties of the ricin molecule.

Diagnosis

The diagnosis of ricin toxicity is challenging. The differential diagnosis includes exposure to staphylococcal enterotoxin, phosgene, oxides of nitrogen, and organohalides. If a bioterrorism attack is suspected, anthrax, plague, and tularemia should also be considered. Ricin intoxication by the inhalational route can be confirmed by ELISA analysis of nasal mucosal swabs taken within 24 hours of exposure. Specific ricin antigen testing or immunochemical staining of serum and respiratory secretions can also be performed. Because ricin is an immunogenic toxin, a significant increase in the antiricin antibody titer 2 weeks after exposure may also be helpful in confirming the diagnosis. It is recommended that acute and convalescent antibody titers be obtained in all individuals suspected of ricin intoxication. However, antiricin antibodies are rapidly metabolized and excreted, so the absence of a significant increase in titer does not exclude the diagnosis [131,153,154].

Neutrophilic leukocytosis is usually present in peripheral blood. Pleural effusions and bilateral alveolar infiltrates, indicative of pulmonary edema, may be seen on chest radiographs. Arterial blood gases should be monitored to assess oxygenation, the adequacy of ventilation, and acid–base status. Myocardial ischemia, cardiac dysrhythmias, and cardiac conduction abnormalities may occur. Therefore, an electrocardiogram and cardiac biomarkers should be obtained. An echocardiogram may be helpful in assessing myocardial contractility if heart failure is suspected [131,155].

Treatment

The management of ricin intoxication is largely supportive, regardless of the route of exposure [130,132,133]. All patients suspected of ricin intoxication should be decontaminated by removing all clothing and washing the skin with soap and water. Careful attention to fluid and electrolyte balance is essential, especially in patients with pulmonary edema. Vasopressors may be needed for the management of severe hypotension. If ricin ingestion has occurred, gastric lavage may be helpful in removing ricin from the gastrointestinal tract. If the patient is alert, activated charcoal can be given. Blood transfusion with packed red blood cells may be needed if severe anemia is caused by bloody diarrhea. If inhalation is the route of exposure, careful airway management is essential. Bronchospasm should be treated with a nebulized bronchodilator. Patients with severe pulmonary edema will require intubation and mechanical ventilation. Oxygen should be administered at a concentration sufficient to keep the arterial oxygen tension (PaO_2) greater than 60 mm Hg. Myocardial infarction, myocardial ischemia, cardiac dysrhythmias, and cardiac conduction abnormalities should be treated as appropriate. A temporary pacemaker may

be required for severe conduction abnormalities, such as complete heart block. Mild allergic reactions can be treated with an antihistamine. Epinephrine should be given for anaphylaxis. A nonsteroidal anti-inflammatory drug can be given for arthralgias and myalgias [131].

There is no specific antitoxin for ricin. Animal studies have shown that active immunization or passive prophylaxis can be effective against the parenteral or intraperitoneal administration of ricin if administered within a few hours following exposure. One animal study showed that the administration of aerosolized antiricin antibody can offer protection against the effects of ricin inhalation. The intratracheal administration of ricin toxoid led to reduction in lung inflammation in another animal study. There are no clinical trials or reports regarding the use of these agents in humans; therefore, their therapeutic efficacy in the clinical setting is unknown [130–133,146].

Most patients with ricin intoxication should survive the acute effects if appropriate supportive care is given promptly after exposure. However, because the clinical effects of ricin intoxication are dose-related, individuals exposed to high concentrations may die from cardiopulmonary arrest in spite of the best supportive care.

Immunization

Animal studies have shown that rats immunized against ricin with formalin-treated toxoids administered subcutaneously survived acute inhalation challenges with lethal doses of ricin [137,156,157]. Another animal study showed that the immunization of mice with an oral ricin-toxoid vaccine encapsulated in polymeric microspheres offered protection against inhalational exposure to ricin [158]. Several studies using a rat model have shown that antibody-mediated immunity to ricin following ricin-toxoid vaccination offered protection against lethal doses of ricin. There are also animal data that indicate that secretory antibodies are important in preventing injury to the lung after an aerosol challenge with ricin. Although ricin-toxoid vaccines have been shown to be protective in animal models, they may not be clinically useful in humans due to safety concerns. Researchers are working on the development of a vaccine against ricin that can be given to humans prior to exposure. The future use of such a vaccine in humans will depend on its safety profile and its efficacy in stimulating protective antibodies against ricin, especially in the mucosal layers of the respiratory and intestinal tracts [131,159–162].

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CHAPTER 214 ■ CHEMICAL AGENTS OF MASS DESTRUCTION

JAMES GEILING AND LAWRENCE C. MOHR JR

If supposedly civilized nations confined their warfare to attacks on the enemy's troops, the matter of defense against warfare chemicals would be purely a military problem, and therefore beyond the scope of this study. But such is far from the case. In these days of total warfare, the civilians, including women and children, are subject to attack at all times.

Colonel Edgar Erskine Hume, Medical Corps, U.S. Army, 1943 [1]

Chemical agents of terror have moved to the forefront of concern for healthcare providers as weapons of mass destruction (WMD) have become readily available to both domestic and international terrorists. Critical care physicians must be familiar with these agents, their impact on patients, and the potential dangers these compounds can cause to healthcare workers.

Although terrorists have traditionally focused their efforts on the use of conventional explosives, chemical agents have emerged as attractive weapons of terrorism for a variety of reasons:

- Raw materials for their production are readily available throughout the world.
- Raw materials are inexpensive.
- A chemical weapon of mass destruction can be produced with relatively small amounts of raw materials.
- They may be odorless, colorless, and tasteless.
- They are poorly detected.
- They do not destroy infrastructure.
- They possess a latency period between the time of exposure and the development of clinical symptoms.
- Their use produces a mass media response [2].

Hospital-based physicians normally, at some time in their medical career, study the skills and procedures needed to treat mass casualties. The focus, however, has traditionally centered on large numbers of casualties presenting to the emergency department as a result of multisystem trauma, such as that sustained in an explosion, airplane crash, or natural disaster. The event of September 11, 2001, and subsequent terrorist threats have changed the nature of physician training and preparation requirements. The scope of preparation now requires knowledge of the mass care of victims following a WMD event. This chapter focuses on the recognition and management of patients exposed to common chemical agents of mass destruction.

HISTORY

Chemical agents of mass destruction are gaseous, liquid, or solid substances that are employed against a population because of their direct toxic effects. Virtually any toxic substance can be used as an agent of mass destruction. However, those that have been successfully weaponized are characterized by ease of production, ease of handling during weapon assembly, dispersion properties, and ability to cause injury and death in relatively low concentrations [3].

Although the first reported use of chemical agents dates back to 1000 BC, when Chinese forces used arsenical smokes, the use of chemical agents in warfare began in earnest during World War I when German forces seeking a breakout from the stalemate of trench warfare released 150 tons of chlorine gas from 6,000 cylinders on the afternoon of April 15, 1915, near Ypres, Belgium. The chlorine gas resulted in 800 deaths and caused the retreat of 15,000 Allied troops, largely because of the psychological terror produced by the gas attack.

The next major use of chemical weapons took place more than 2 years later, on July 12, 1917, again near Ypres. On that date, German forces attacked Allied troops with artillery shells containing sulfur mustard. This attack resulted in 20,000 casualties. Although many casualties had debilitating injuries, less than 5% of the troops died as a result of the chemical attack. Persistent and nonvolatile, sulfur mustard caused a host of new problems for Allied forces, including a latency period before the effects appeared and the need for men, and their horses, to wear protective overgarments [4].

The Geneva Convention of 1925 banned the use of chemical warfare agents because of the physical and psychological trauma they imposed on their victims.

Nerve agents appeared in the 1930s when the German industrial chemist, Dr. Gerhard Schrader, began research into the development of stronger insecticides, the first two of which were tabun and sarin. German forces stockpiled these for use in World War II, but never used them.

Chemical agents were used sporadically in the second half of the twentieth century. The United States used defoliants and riot-controlled agents in Vietnam. Iraq used mustard, tabun, and eventually sarin against Iran in the Iran–Iraq war of the 1980s. Later in the 1980s, reports implicated Iraq in the use of cyanide against the Kurdish population in northern Iraq [5].

The most recent publicized use of chemical agents took place in Japan when the Aum Shinrikyo religious cult released sarin gas on two occasions. The first took place on June 27, 1994, in Matsumoto and resulted in 600 persons exposed, 58 admitted to the hospital, and 7 deaths [6]. The more famous and larger event took place the following year, on March 20, 1995, when the cult released sarin gas in the Tokyo subway system during rush hour. The subway system attack resulted in the deaths of 11 commuters and the medical evaluation of approximately 5,000 individuals [7].

In 1997 the Chemical Weapons Convention (CWC) went into effect as an international treaty that bans the use, development, production, acquisition, transfer, stockpiling, and retention of chemical weapons by signatory nations. At the time of this writing, the CWC was ratified by 175 nations, including the United States. The CWC is administered by the Organization for the Prohibition of Chemical Weapons, which conducts regular inspections and monitors compliance with provisions of the treaty [8].

DETECTION AND DECONTAMINATION

Initial steps in the management of chemical agent casualties include detection of the chemical agent used in the attack and the decontamination of casualties. Detailed discussions on detection and decontamination are beyond the scope of this chapter. However, hospital-based critical care physicians should understand basic concepts of these topics to better care for their patients and protect themselves and their facilities from potential harm.

The most important tool in detecting the use of these agents is accurate and timely intelligence from military or law enforcement agencies. Unfortunately, hospitals are not usually in the information-sharing and decision-making circles with these groups. As a result, initial awareness of a chemical agent attack typically occurs with the first patient presenting to the emergency department. Hospitals and physicians can improve their preparedness for the management of chemical agent casualties by actively participating in disaster-planning activities in their respective communities.

Various types of sensing devices can be used for the detection of chemical agents in the environment. At the present time, all commercially available detection equipment uses point source technology; that is, proximity to the substance is required. The handheld Chemical Agent Monitor uses ion mobility spectrometry to detect mustard and nerve agents. Chemical agent detection papers, such as the M8 and M9 papers (Anachemia, Lachine, Quebec, Canada), can be used to detect mustard and nerve agents. The M256 Detection Kit (Anachemia, Lachine, Quebec, Canada) can detect mustard, nerve agents, phosgene, and cyanide. Standoff capability, that is, detecting agents from as far away as 5 km, has been developed to detect contaminated areas without being exposed [9]. Newer chemical agent detection technologies will continue to evolve in response to the terrorism threat. These can only help ensure hospitals and providers have quicker, more accurate information to meet the needs of victims.

Ideally, the decontamination of chemical agent casualties should be accomplished by first responders or hazardous material personnel prior to evacuation or transport to a medical facility. Unfortunately, most disaster victims bypass emergency medical system transport and arrive unannounced at the closest hospital. As a result, hospitals must be prepared to decontaminate chemical agent casualties prior to admission. Facilities and protocols to decontaminate such casualties should be developed by all hospitals. Such processes are needed to protect the victims from further exposure and to prevent the spread of chemical agents within the hospital and among healthcare providers. Critical care physicians, nurses, and support personnel may be called on to help develop decontamination protocols and assist in the decontamination process. It is imperative that all individuals designated to serve on decontamination teams be thoroughly trained in the procedures, precautions, and protective clothing required in the decontamination process. Attempting to provide help in a contaminated environment without prior training puts the healthcare provider at risk of being exposed to a chemical agent and could impede the delivery of effective medical care for the victims of a chemical attack.

The sarin gas release in Tokyo provides a clear example of the need for preparation and training prior to a chemical attack. Of the 1,364 emergency personnel who responded to the attack, 135 (9.9%) became symptomatic and required medical support themselves. None of the first responders wore protective clothing or face masks and off-gassing of the chemical agent from clothing of victims played a significant role in their complaints. These effects were evident among hospital staff as well first responders. It was reported that 23% of the staff at the hospital that received the patients also experienced symptoms [10].

The Occupational Safety and Health Administration (OSHA) mandates that all healthcare providers be trained to perform their duties without jeopardizing the health and safety of themselves or coworkers. It provides guidance for the use of personal protective equipment and requires that written plans be developed for hospitals to train teams in the use of personal protective equipment to receive contaminated victims [11]. Most medical facilities prepare their decontamination teams to operate in OSHA personal protective equipment Level C; that is, full-face mask with an air-purifying canister respirator and chemical-resistant clothing.

In most situations, effective chemical decontamination can be performed by carefully removing the victim's clothing and thoroughly washing the victim with soap and water. It has been reported that removing contaminated clothing alone can eliminate 85% to 90% of chemical contaminants [12]. Recently developed for the military and soon to be used by first responders is Reactive Skin Decontamination Lotion (RSDL) (O'Dell Engineering Ltd/E-Z-EM Canada Inc., Canada). It is not used for prophylactic protection or total body decontamination, but, if applied early following exposure, is effective in neutralizing chemical warfare agents and T2 mycotoxins [13]. However, in exposures associated with trauma, RSDL may interfere with normal wound healing [14]. EasyDECON (Envirofoam Technologies, Huntsville, Alabama) can be used to decontaminate exposed environmental surfaces. Normally employed as a foam, it effectively neutralizes a variety of chemical agents including nerve gases and mustard [15]. Finally, medical facilities must consider environmental variables such as wind direction, wind velocity, temperature, and water runoff when setting up decontamination areas. These environmental considerations are important in protecting patients and employees from exposure to chemical agents, as well as minimizing the risk of contaminating buildings and equipment during the patient decontamination process.

CLASSIFICATION OF CHEMICAL AGENTS

Chemical agents are normally classified into broad categories based on their mechanisms of action and physiologic effects. The most common classification scheme divides them into the following categories:

- Nerve agents
- Vesicants
- Cyanide agents or "blood" agents
- Pulmonary agents or "choking" agents
- Nonlethal incapacitating agents

Nerve Agents

Because they are the most toxic, nerve agents are the most feared of chemical agents. All nerve agents are organophosphorus compounds, which inhibit butyrylcholinesterase in the plasma, acetylcholinesterase in the red blood cell (RBC), and acetylcholinesterase at cholinergic receptor sites in the central and peripheral nervous systems. The chemical bond between nerve agent molecules and acetylcholinesterase is irreversible; thus, acetylcholinesterase activity returns only with new acetylcholinesterase synthesis or RBC turnover (1% per day) [16]. The decrease in acetylcholinesterase activity results in the accumulation of acetylcholine at both muscarinic and nicotinic

receptors in the central nervous system and neuromuscular junctions of the peripheral nervous system. Cholinergic overstimulation resulting from the accumulation of excess acetylcholine in the central and peripheral nervous systems is responsible for the clinical manifestations of nerve agent toxicity [17].

After an acute exposure to nerve agents, RBC acetylcholinesterase reflects nervous system acetylcholinesterase activity better than the activity of butyrylcholinesterase in the plasma. The measurement of RBC acetylcholinesterase activity is principally a research tool at the present time, and it is not useful in the management of mass casualties from nerve agent exposure. However, its measurement in blood samples collected from victims of a chemical attack may be useful in forensic investigations.

Several different nerve agents currently exist, each characterized by a unique molecular structure that irreversibly inhibits acetylcholinesterase. Compounds that were originally developed in Germany have been designated as the "G" series of nerves agents. The "V" series of agents are better absorbed through the skin than the "G" agents and are so designated because they are more "venomous." The most common nerve agents include:

- GA (tabun): ethyl N,N-dimethylphosphoramidocyanidate
- GB (sarin): isopropyl methyl phosphonofluoridate
- GD (soman): pinacolyl methyl phosphonofluoridate
- GF: O-cyclohexyl-methylphosphonofluoridate
- VX: O-ethyl S-(2-(diisopropylaminoethyl) methyl phosphonothiolate

The "G" agents are volatile, whereas VX is a persistent, oily substance with better percutaneous absorption. Each of these agents can be dispersed through a variety of weapons and munitions.

Inhalation of nerve gas is the most effective means of producing clinical effects, although it can also be ingested. High doses of persistent nerve agents, such as VX, can be absorbed through the skin. The clinical effects of nerve agent toxicity occur as a result of acetylcholine accumulating at both nicotinic sites (autonomic ganglia and skeletal muscle) as well as muscarinic sites (including postganglionic parasympathetic fibers, glands, and pulmonary and gastrointestinal smooth muscles). Nicotinic receptors appear to be most sensitive to the effects of nerve agents, with inactivation of acetylcholinesterase in autonomic ganglia and the neuromuscular junction of skeletal muscle responsible for many symptoms and signs of nerve agent exposure. The typical clinical manifestations of nerve agent toxicity are similar to those produced by organophosphate insecticides, although nerve agents are up to 1,000 times more toxic [17].

The basic clinical syndrome produced by nerve agents can be remembered by the acronym "SLUDGE": salivation, lacrimation, urination, defecation, gastric distress, and emesis. Alternatively, "DUMBELS" (diarrhea, urination, miosis, bradycardia/bronchorrhea/bronchospasm, emesis, lacrimation, salivation/secretion/sweating) provides a more detailed tool to remember the muscarinic signs and symptoms [18]. Specific signs and symptoms in various organ systems depend on the dose of nerve agent received. Inhalation of a nerve agent usually produces immediate effects that occur within seconds to minutes after exposure. Dermal absorption usually produces delayed effects that can develop at any time between 10 minutes and 18 hours after skin exposure, depending on the dose. Common signs and symptoms in each organ system are summarized here.

Inhalation of a nerve agent typically results in the development of rhinorrhea, bronchorrhea, and bronchoconstriction soon after exposure. Dyspnea and chest tightness are common early symptoms. Coughing and wheezing may occur. The volume of airway secretions, the magnitude of bronchoconstriction, and the severity of airway symptoms all increase with higher exposure doses. High-dose or prolonged exposure may result in diaphragmatic weakness and centrally mediated apnea, which can result in ventilatory failure [16,17].

Although vagally mediated bradycardia is the expected heart rate response from cholinergic overstimulation of muscarinic receptors, this is commonly overridden by tachycardia resulting from nicotinic-mediated adrenergic stimulation and hypoxia. First-, second-, and third-degree heart block may occur [16,17]. Prolongation of the QTc interval can precipitate Torsade de pointes that has a poor prognosis [19]. Although hypertension may occur as a result of nicotinic-mediated adrenergic stimulation, blood pressure usually remains normal. A decline in blood pressure is typically a sign of impending death [4].

Muscarinic and nicotinic stimulation of the peripheral nervous system typically results in muscle fasciculations and profuse sweating, respectively. Muscle weakness and muscle paralysis may occur following high-dose exposures. Seizures can develop suddenly. The seizures may resolve spontaneously, but can be prolonged with status epilepticus [16,17]. Smaller-exposure doses typically result in nonspecific neurologic findings including an inability to concentrate, insomnia, irritability, and depression. A variety of psychological and behavioral changes, ranging from mild confusion to severe anxiety, can also occur [15]. Hallucinations or complete disorientation do not appear. Mild exposure also may result in a slight decline in memory function, as observed in first responders in the Tokyo sarin gas release of 1995 [20]. In the decade since that event, those exposed continue to have mild cerebellar effects and principally posttraumatic stress disorder [21].

Direct contact of the eyes with nerve agent vapor causes miosis that is usually associated with intense ocular pain. Patients also complain of blurred or dim vision and typically have injected conjunctivae with significant lacrimation.

Nausea and vomiting may be among the first signs of nerve agent toxicity. Abdominal cramping and diarrhea may also occur [16,17].

Unfortunately, few of the clinical signs or symptoms listed here may appear following exposure to a high dose of nerve agent. This is due to the fact that the range of exposure of doses, which produce clinical symptoms, is only slightly less than those which cause death. Therefore, central nervous system collapse with seizures, loss of consciousness, and central apnea may be the first signs of nerve agent toxicity following a high-dose exposure [16].

Management of all nerve agent casualties begins with the traditional "ABCs" of resuscitation: airway, breathing, and circulation support. Contaminated patients should be managed in the following order:

- Airway management
- Breathing support
- Circulation and hemorrhage control
- Antidote administration
- Decontamination
- Wound dressing
- Evacuation to a noncontaminated treatment location [22]

Ventilatory failure is the primary cause of death following nerve agent exposure [23]. As a result, airway management and breathing support are extremely important in the management of nerve agent casualties. The nausea and vomiting that these patients typically experience must be considered in their airway management. In this regard, all patients should be considered to have a full stomach. Endotracheal intubation and assisted ventilation are required for the management of ventilatory failure. High airway resistance necessitating the need of pressures up to 50 to 70 cm of water may complicate ventilatory support [17]. Because of high airway pressures, if a cuffed endotracheal tube cannot be placed, a double-lumen Combitube (Tyco

Healthcare, Pleasanton, CA) is preferable to a laryngeal mask airway [24]. Once an effective airway has been established, ventilatory assistance can be provided by manual ventilation using a bag-valve device or by mechanical ventilation. Nebulized ipratropium can be used for the treatment of bronchospasm that may, in turn, result in decreased airway resistance [16]. Frequent suctioning is necessary to remove the copious airway secretions associated with nerve agent exposure. The use of depolarizing neuromuscular blocking agents during ventilatory assistance should be avoided [25].

The principal antidote for nerve agents is atropine. Atropine is an anticholinergic drug that blocks acetylcholine receptor sites. As a result, atropine blocks the pathophysiologic effects of the excess acetylcholine that accumulates as a result of nerve gas exposure; it is most effective at muscarinic sites. Atropine is primarily used for the purpose of drying up the copious airway secretions that patients develop following nerve agent exposure. The standard adult dosing regimen is 2 mg, administered intramuscularly, every 5 to 10 minutes, titrated to the patient's secretions. The recommended pediatric dose is 0.05 mg per kg, with a minimum dose of 0.1 mg, administered intravenously every 2 to 5 minutes, titrated to effect [17,23]. In severe cases, adult patients may require 10 to 20 mg of atropine in the first hour to control secretions. The administration of atropine to a hypoxemic patient could precipitate the development of ventricular fibrillation. Therefore, oxygen should be administered and hypoxemia corrected before atropine is given [22,26]. Miosis will not respond to parenteral atropine. Topical tropicamide is effective for the treatment of miosis and the relief of ocular pain [23]. Atropine alone may not be an effective treatment for terminating seizures or reversing ventilatory failure [17,26]. Bulk atropine is available for reconstitution and may be required in the setting of mass nerve agent casualties.

Pralidoxime chloride is the other major antidote for nerve agents. It functions by "prying off" the nerve agent molecule from acetylcholinesterase, thereby rendering the enzyme active again. Unfortunately, it must be given early, before the agent–enzyme bond matures or "ages," that occurs in as little as 2 minutes for soman but takes 3 to 4 hours for sarin. Once the agent–enzyme bond completely ages, the bond is irreversible and pralidoxime chloride has no therapeutic effect. Pralidoxime chloride is only effective at nicotinic sites and, therefore, helps to increase muscle strength. The standard adult dose is 15 to 25 mg per kg or 1 g, given intravenously (in 100 to 250 mL of 0.9% saline) during 20 to 30 minutes. The initial dose may be followed by an infusion of 200 to 500 mg per hour, if necessary. Higher dosing with a 2 g load followed by 1 g per hour for 48 hours has been shown to significantly decrease atropine requirements and the duration of mechanical ventilation in patients poisoned by organophosphate pesticides [27]. Severe hypertension is a potential side effect of pralidoxime chloride, and this can be rapidly reversed by a 5-mg intravenous infusion of phentolamine. The recommended pediatric dose is 15 to 25 mg per kg administered intravenously during 30 to 40 minutes [23].

Atropine and pralidoxime chloride come packaged as two autoinjectors in commercially available kits, called MARK-I Nerve Agent Antidote Kits (Meridian Medical Technologies, Columbia, MD). Each kit contains one AtroPen Auto-Injector containing 2 mg of atropine and one pralidoxime chloride Auto-Injector containing 600 mg of pralidoxime chloride. The same company also now produces DuoDote^{TM}, a single autoinjector 2.1 mg of atropine and 600 mg of pralidoxime chloride [28].

Historically, diazepam has been the anticonvulsant recommended for the management of seizures associated with nerve agent exposure. In the hospital setting, diazepam may be given intravenously. The adult intravenous dose is 5 to 10 mg every 10 to 20 minutes until seizures resolve, but not to exceed 30 mg in an 8-hour period. The pediatric dose is 15 to 25 mg per kg [23]. Autoinjectors that contain 10 mg of diazepam are available for use in the field (Meridian Medical Technologies). In both hospital and prehospital settings, healthcare providers must carefully monitor patients for signs of ventilatory failure following the administration of diazepam. Lorazepam and midazolam that are typically used in a critical care environment are also effective in controlling seizures following nerve agent exposure [29,30].

Decontamination is a key step in the treatment of nerve agent casualties because minimizing exposure to the agent decreases the severity of toxic effects. Removal of all clothing, rinsing the eyes with water or normal saline for 10 minutes, and washing the entire body once with soap and water should suffice. Decontamination should be conducted as soon as possible after ventilatory and circulatory support has been initiated and antidotes have been administered. Rapid decontamination is especially important for nerve agents that can be absorbed through the skin. It is important for healthcare providers to wear protective clothing and face masks prior to and during contamination of nerve agent casualties [10,16].

Vesicants

The two principal vesicants or "blister agents" are sulfur mustard and lewisite. This section focuses on the more notable sulfur mustard (bis-[2-chloroethyl] sulfide) that is commonly referred to as *mustard*. Lewisite has similar health effects except for the immediacy of its action in comparison to mustard, which has a latency period. It normally takes several hours between contact with mustard and the onset of signs and symptoms, with the specific latency period depending on the exposure dose. In general, the higher the exposure dose, the shorter the latency period. Mustard is an oily liquid that ranges from clear to pale yellow to dark brown in color. It classically smells like onion, garlic, or mustard, which is allegedly how it got its name. At temperate conditions, it is a persistent liquid that volatilizes slowly. At temperatures greater than 100°F, however, mustard evaporates and mustard vapor becomes a major hazard. As a weapon, mustard will most likely be employed as a contact agent [31].

On entering living cells, mustard alkylates and cross-links DNA that causes DNA strand breaks and eventually leads to cell death. Mustard damages any skin that it contacts, resulting in vesicle or bullae formation within 4 to 24 hours after exposure. Vesicle formation typically peaks within several days after contact with the skin; of note, the bullae fluid is not toxic and therefore not a threat to providers. As the most sensitive organ to low dosage exposures, contact with the eyes may result in painful irritation, conjunctivitis, blepharospasm, and corneal opacity related to edema and pannus formation. Blindness can occur if the corneal pannus is severe and covers the visual axis. Eyelid burns may be first or second degree. Mild-to-severe airway damage can occur following mustard inhalation. The extent and severity of airway damage is dose-dependent, with lower doses primarily affecting the upper airways and higher doses affecting both upper and lower airways. At all doses, the proximal and upper airways are affected more than lower airways. High inhalational doses can cause severe inflammation, inflammatory exudate, necrosis of mucous membranes, mucosal sloughing, and pseudomembrane formation. Sloughed mucosal tissue and pseudomembranes can cause obstruction of the lower airways and serve as a nidus for respiratory tract infections, principally *Pseudomonas*. Other pulmonary problems include asthma, laryngospasm, acute bronchitis, chronic bronchitis, bronchiectasis, tracheobronchial stenosis, pulmonary fibrosis, and bronchiolitis obliterans [32,33]. Hypoxia and hypercarbia may occur as a result of ventilation-perfusion

mismatching caused by airway mucosal sloughing and hyperreactive or bronchitic airways. Severe gastrointestinal side effects and bone marrow suppression can occur following ingestion of high doses of mustard. Leukopenia with a cell count less than 200 cells per mm^3 portends a poor prognosis. Sepsis may occur as a result of leukopenia and the breakdown of skin, respiratory epithelium, and gastrointestinal mucosa [34].

Decontamination is a critical component in the management of mustard casualties. Indeed, decontamination within 1 to 2 minutes after exposure is the most effective means of reducing serious skin and tissue damage from mustard. Because of its persistence, removal of mustard from casualties must occur before admission to a medical treatment facility so healthcare workers do not become contaminated. In general, the medical care of mustard casualties is supportive. Areas of denuded skin should be treated like burns and liberally covered with silver sulfadiazine ointment [12]. Calamine lotion may soothe mild burning and itching in erythematous areas of skin. Nonsteroidal anti-inflammatory drugs may help to mitigate pain associated with cutaneous inflammation. Cooling the skin to 15° C and applying deferoxamine or zinc oxide may also be beneficial [35]. Skin healing following mustard exposure takes longer than skin healing following thermal burns. Some patients may require skin grafts and reconstructive surgery.

Respiratory care is mostly supportive. Bronchodilators may be helpful for the treatment of asthma-like symptoms related to hyperreactive airways. Corticosteroids may also be helpful, but should be used with caution because of the risk of superinfection. Intubation and ventilatory support may be necessary for the management of severe laryngospasm or respiratory failure following high doses of inhaled mustard. Bronchoscopy may be necessary to remove pseudomembrane fragments from the airway. Chronic, progressive tracheobronchial stenosis has been reported following mustard inhalation, and may require periodic bronchoscopy with bougienage and laser photoresection to maintain airway patency [36].

For systemic toxicity, early treatment with nonsteroidal anti-inflammatory agents may be useful. Thiosulfate decreases toxicity in animals; also in animal models, granulocyte colony stimulating factor has been shown to reduce the duration of neutropenia by approximately half [37].

In summary, acute mortality is relatively low, but morbidity is high following exposure to mustard. The severity and duration of illness and injuries following mustard exposure are directly related to the exposure dose and routes of exposure. Because of the persistence of mustard, decontamination is critically important in the management of mustard casualties and for protecting healthcare workers from being exposed. Victims of mustard exposure will consume significant healthcare resources in the management of their acute care needs and some will require prolonged periods of treatment and rehabilitation for chronic sequelae.

Cyanide

Cyanide can exist either as gas or as a colorless, volatile liquid that easily vaporizes. In both physical states, it typically has the smell of bitter almonds, although 40% to 60% of the population is unable to detect this odor. It is a chemical asphyxiant of the type that is historically classified as a "blood" agent. Cyanide can be used as an agent of mass destruction in two chemical forms: hydrogen cyanide and cyanogen chloride. Although very lethal in high doses, the volatility of cyanide makes it difficult to weaponize and it ranks among the least lethal of the common chemical agents of mass destruction. Cyanide produces its pathologic effects by binding to iron-containing sites on cytochrome a_3 in the mitochondria that inhibits the enzyme's activity. The binding of cyanide to cytochrome a_3 can occur very rapidly. Cytochrome a_3 is a key enzyme in the cytochrome oxidase system involved in aerobic metabolism within the mitochondria of cells. Inhibition of cytochrome a_3 by cyanide effectively stops cellular respiration and forces affected cells into anaerobic metabolism. Cyanide also has an increased affinity for the ferric ion in methemoglobin that is a property exploited for treatment of cyanide poisoning [38].

The clinical manifestations of cyanide poisoning result from the inability of cells to extract and use oxygen. The onset of signs and symptoms occurs rapidly following inhalation (within 15 seconds), whereas a delayed response of up to 30 minutes follows ingestion. Metabolic acidosis develops as a consequence of increased lactate production from anaerobic metabolism. Compensatory mechanisms to increase oxygen delivery to tissues include tachycardia and increased minute ventilation, which are the earliest clinical signs. Dyspnea may occur as a result of the hyperpnea. Other signs include agitation, anxiety, vertigo, headache, muscle weakness, and trembling. Diaphoresis and flushing sometimes occur. Seizures have been reported. Dilated, unresponsive pupils and coma are late signs of cyanide poisoning and portend a poor prognosis. Without treatment, cyanide victims eventually develop apnea and cardiac dysrhythmias, followed by death from cardiac arrest [38].

Both the administration of specific antidotes and supportive care should be given as soon as possible after exposure to cyanide. Sodium nitrite and sodium thiosulfate are the traditional antidotes used to treat cyanide poisoning. This treatment's objectives focus on detoxifying and excreting the cyanide, as well as on preventing its reentry into the cell. One ampule containing 300 mg of sodium nitrite in 10 mL of diluent (30 mg per mL) is administered intravenously for 2 to 4 minutes to form methemoglobin. The pediatric dose of sodium nitrite is 0.33 mL per kg of a 3% solution given intravenously for 2 to 4 minutes, not to exceed 10 mL. Cyanide binds more effectively and preferentially to the ferric ion site on methemoglobin in comparison to cytochrome a_3. Therefore, the methemoglobin generated by sodium nitrite removes cyanide from cytochrome a_3-binding sites and frees the enzyme to once again participate in the processes of cellular respiration and aerobic metabolism. Following sodium nitrite administration, 12.5 g of sodium thiosulfate in 50 mL of diluent is administered intravenously at a rate of 3 to 5 mL per minute. The pediatric dose of sodium thiosulfate is 412.5 mg per kg (1.65 mL per kg), given intravenously at a rate of 3 to 5 mL per minute. Sodium thiosulfate acts as substrate for rhodanese, converting the cyanide to thiocyanate that is then excreted in the urine. Sodium nitrite and sodium thiosulfate are very effective antidotes for the treatment of cyanide poisoning if they are given before the cessation of cardiac activity [38,39].

A specific challenge in managing these patients is in the prehospital environment, specifically in hypoxia environments such as fires or smoke, inhalation where decreased oxygen-carrying capacity can be exacerbated by the induction of methemoglobinemia. Hydroxocobalamin, a precursor of vitamin B_{12}, provides an alternative treatment option for both pre- and in-hospital management. Cyanokit® (Dey L.P., Napa CA., www.cyanokit.com) contains two vials of 2.5 g of lyophilized hydroxocobalamin that is reconstituted in 100 cc saline for administration. The standard initial adult dose is 5 g infused over 15 minutes with an additional 5 g given depending on the patient's condition. Hydroxocobalamin binds with cyanide to form cyanocobalamin that is then excreted in the urine. It is well tolerated with no known major toxicities. Of note, the red molecule results in red mucous membranes, skin, and urine [40]. A major impediment to widespread use of this modality is its cost which is over twice as expensive as the sodium nitrite/sodium thiosulfate kit [41].

Supportive care for cyanide poisoning includes the administration of oxygen that has been shown to be effective in managing hypoxia, even though the poor cellular uptake and

utilization of oxygen found in cyanide toxicity would suggest supplemental oxygen to be of little efficacy. Hyperbaric oxygen may also be beneficial in select severely ill patients, though this therapy would be difficult to institute in a mass casualty setting [12]. Ventilatory support should be provided as needed. Consideration should be given to the administration of sodium bicarbonate for the treatment of severe lactic acidosis in patients who are unconscious or hemodynamically unstable. The recommended dose of sodium bicarbonate intravenously is 1 to 2 mg per kg intravenously, for both adults and children. Arterial blood gas analysis is used to guide the need for repeat doses of sodium bicarbonate to ensure that a metabolic alkalosis does not develop. In most cases of cyanide poisoning, appropriate supportive care in conjunction with the administration of sodium nitrite and sodium thiosulfate or hydroxocobalamin before cardiac arrest occurs can result in a complete recovery over a period of several days [38,40,42].

Pulmonary or "Choking" Agents

Pulmonary or "choking" agents cause acute lung injury after inhalation. The acute lung injury produced by these agents typically results in the development of pulmonary edema. Phosgene and chlorine are the two most common chemical agents in this category. Both were used as chemical warfare agents in World War I. Their effects relate, in part, to their water solubility. Highly water-soluble gases like ammonia, hydrogen chloride, and sulfur dioxide affect primarily the eyes and upper airway mucous membranes. Chlorine, a moderately water-soluble gas, affects the upper airway less but also damages the lower airway. Finally, slightly water-soluble gases like phosgene affect primarily the lower airways.

Phosgene is a colorless gas at room temperature, but becomes a volatile liquid on cooling or compression. The gaseous form has an odor of green corn or freshly mown hay. The gas is denser than air and accumulates in low-lying areas. On exposure to water, phosgene hydrolyzes to form carbon dioxide and hydrochloric acid. These hydrolyzation products may cause phosgene gas to appear as a white cloud when it comes into contact with water vapor in the air [43].

Initial symptoms of phosgene poisoning are primarily related to inflammatory irritation of the eyes and mucous membranes of the oronasopharynx. The irritation is caused by the hydrochloric acid that is formed when phosgene reacts with tissue water. Initial symptoms occur shortly after exposure and include burning sensation in eyes, conjunctival erythema, increased lacrimation, soreness of the throat and nasal membranes, rhinorrhea, coughing, choking, and tightness in the chest. Nausea, occasional vomiting, and headache have also been reported to occur shortly after phosgene exposure. These may be the only symptoms that occur following a low-concentration exposure. However, a life-threatening illness, characterized by noncardiogenic pulmonary edema and respiratory failure, can develop after exposure to higher concentrations.

Inhaled phosgene causes the formation of hydrochloric acid in the airways and alveoli that causes direct inflammatory injury to epithelial cells and endothelial cells of pulmonary capillaries. In addition, phosgene causes an acylation reaction with amino, hydroxyl, and sulfhydryl groups on cellular macromolecules, resulting in oxidative injury to lung tissues. It also stimulates the synthesis of lipoxygenase-derived leukotrienes that results in the chemotactic attraction of neutrophils and their accumulation in the lung. In the lung, the damaged alveolar-capillary membrane leads to pulmonary edema. This effect only occurs through direct inhalation.

As noted earlier, inhaled phosgene affects primarily the lower respiratory tract, causing diffuse bronchoalveolar injury, bronchospasm, and noncardiogenic pulmonary edema. Exertion tends to decrease the latency period between phosgene inhalation and the development of pulmonary symptoms, as well as exacerbate pulmonary symptoms once they occur. Phosgene-produced pulmonary edema may begin as early as 2 to 6 hours after inhalation. Although the pulmonary edema may appear to be mild at first, it can become extensive and life threatening. Normal pulmonary lymphatic drainage may be overwhelmed by increasing pulmonary edema that leads to the development of the acute respiratory distress syndrome (ARDS) in some individuals. The onset of ARDS may be delayed for up to 48 hours after phosgene inhalation [44].

Chlorine is a greenish-yellow, noncombustible gas at room temperature and normal atmospheric pressure. It is heavier than air and gravitates to low-lying areas if released in the environment. Chlorine has a strong, pungent odor similar to bleach that is usually detectable by smell, even in low concentrations. It is a highly reactive element and, like phosgene, forms hydrochloric acid on contact with water [43].

Initial symptoms of chlorine exposure are similar to the initial symptoms following exposure to phosgene. Again, these symptoms are caused by irritation produced by the hydrochloric acid that is formed when chlorine comes into contact with tissue water. Initial symptoms occur within minutes after exposure and include burning of the eyes, redness of the conjunctivae, increased lacrimation, soreness of the throat and nasal membranes, rhinorrhea, coughing, choking, and tightness in the chest. Burning and blistering of the skin can occur shortly after contact of chlorine with exposed areas [45].

Inhalation of chlorine, even in low concentrations, causes immediate coughing and choking that can be severe. The coughing and choking tend to prevent some of the inhaled chlorine from reaching the peripheral airways and lung tissue. Thus, inhaled chlorine typically affects the upper airway primarily, causing laryngeal edema, laryngospasm, and bronchospasm. Hoarseness and aphonia may occur. Dyspnea is the first sign of upper airway involvement, followed by copious secretions, productive cough, and chest tightness. Wheezing typically occurs with bronchospasm. Individuals with a history of asthma or airway hyperactivity may have particularly severe bronchospasm. Severe bronchospasm may cause mediastinal and subcutaneous emphysema secondary to air trapping. Inhalation of high concentrations of chlorine may produce laryngospasm that is severe enough to cause sudden death [43].

Noncardiogenic pulmonary edema can occur within 2 to 4 hours following the inhalation of chlorine, especially in high concentrations [46]. Frothy sputum and rales may be the first clinical signs of pulmonary edema. Radiographic signs of pulmonary edema typically lag behind the development of clinical symptoms [47]. The development of ARDS with hypoxemic respiratory failure may eventually occur. The fluid losses associated with severe pulmonary edema and ARDS can be so profound that hypovolemic shock develops.

Management of individuals exposed to inhaled phosgene and chlorine is essentially the same. There is no specific antidote for either agent and treatment is supportive. In all cases, the patient must be removed from the contaminated environment and contaminated clothing as soon as possible. Decontamination should be performed by washing the patient with soap and copious amounts of water for 3 to 5 minutes. The eyes should be flushed with normal saline. Exertion should be minimized during transport and hospitalization.

Aggressive bronchodilator therapy with a nebulized β_2 agonist is the mainstay of therapy for bronchospasm. Nebulized ipratropium may be added if the β_2 agonist alone is ineffective. Systemic corticosteroids may be useful in the treatment of severe bronchospasm, particularly in individuals who have a history of asthma or airway hyperreactivity. Animal studies have shown that inhaled corticosteroids improve oxygenation and attenuate the development of acute lung injury, especially when

given in conjunction with an inhaled bronchodilator [48]; this has not, however, been validated in humans. Thus, although systemic corticosteroids are recommended for life-threatening situations, there is no definitive clinical evidence for their efficacy in reducing the severity of acute lung injury or pulmonary edema.

Bacterial superinfection of the airways can lead to the development of severe tracheobronchitis and pneumonia 3 to 5 days after toxic irritant exposure. The presence of persistent fever, elevated white blood, or the production of thick, purulent sputum should prompt the physician to obtain cultures of sputum, blood, and any pleural fluid that is evident on chest radiograph. Empiric antibiotics should be given in accordance with the guidelines for intensive care unit patients with community-acquired pneumonia. The antibiotic regimen should be adjusted on the basis of the culture and antibiotic sensitivity results [43].

Intubation and mechanical ventilation may be required for severe bronchospasm, laryngospasm, and pulmonary edema. They are usually required for the management of ARDS and respiratory failure. Given the rapidity with which these problems can develop, preparations for intubation and mechanical ventilation should take place during the latency period, before serious respiratory problems develop. Nasotracheal intubation should not be performed because of nasal inflammation. Orotracheal intubation under direct visualization of the airways is the recommended technique. During mechanical ventilation, an appropriate amount of positive end-expiratory pressure, typically in the range of 5 to 10 cm H_2O, and inverse ratio ventilation may be helpful in improving oxygenation in patients with pulmonary edema or ARDS (see Chapters 47 and 58). In animal models, protective ventilation strategies with 6 mL per kg tidal volumes improve oxygenation, decrease shunt fraction, and improve mortality [49].

Careful attention must be given to fluid balance and the administration of intravenous fluids in patients with pulmonary edema and ARDS. Vasopressors may be required for the treatment of hypovolemic shock. Both ibuprofen and acetylcysteine aerosol have demonstrated some efficacy in preventing phosgene-induced lung injury in animal models, although there are no human clinical trials regarding their use [50,51].

Pulmonary edema that appears within 4 hours after phosgene or chlorine exposure is a poor prognostic sign. Some individuals may develop the reactive airways dysfunction syndrome (RADS) following phosgene or chlorine inhalation [52,53]. This disorder is characterized by chronic, nonspecific airway hyperreactivity that persists after the patient has recovered from the effects of an acute exposure. Patients who develop RADS should receive prompt treatment with oral prednisone (40 to 80 mg daily for 10 to 15 days) followed by treatment with a high dose of an inhaled corticosteroid, such as beclomethasone (2,000 µg per day). RADS patients should be followed closely with serial methacholine bronchial challenge testing, and the dose of oral corticosteroid should be tapered in accordance with improvements in airway hyperresponsiveness. It may take years for some individuals with RADS to show significant improvement in airway hyperresponsiveness [54]. However, most individuals who survive phosgene or chlorine exposure will recover completely with no long-term effects [43].

Nonlethal Incapacitating Agents

Chemical agents that cause temporary incapacitation are commonly classified as nonlethal agents. These chemical agents, although potentially lethal in high concentrations, are typically employed in doses that cause temporary injury or confusion to individuals or groups of individuals. They are commonly used to incapacitate unruly groups in military or riot control situations. However, they could be used in a terrorist attack. In this regard, they could be used alone, they could be used prior to an attack with conventional weapons, or they could be used in conjunction with other chemical, biological, or radiological agents of mass destruction.

The most common incapacitating agent is BZ (QNB; 3-quinuclidinyl benzilate), a competitive inhibitor of acetylcholine at postsynaptic and postjunctional muscarinic receptors. BZ is a stable, odorless, persistent crystalline solid. It is usually dispersed as a fine solid powder, although it can be dissolved in a liquid substrate and dispersed as a liquid aerosol. Both the powder and aerosolized forms can be readily ingested or inhaled. Ingestion and inhalation of BZ particles that are 1 µm in size result in bioavailabilities that are approximately 80% and 50% of a parental dose, respectively [55].

The clinical effects of BZ are similar to those of atropine, although BZ is approximately 25 times more potent and has a much longer duration of action. Symptoms of BZ exposure include mydriasis, blurred vision, dry mouth, indistinct speech, dry skin, increased deep tendon reflexes, poor coordination, decreased level of concentration, illusions, and short-term memory deficits. The most prominent central nervous system effects of BZ are related to so-called "anticholinergic delirium." The delirium typically occurs after high-dose BZ exposure and has been described as a "walking dream." This syndrome is characterized by periods of staring, unintelligible muttering, occasional shouting, and bizarre hallucinations. The degree of delirium can fluctuate frequently from minute to minute, with periods of lucidity and appropriate responses interspersed among periods of severely altered mental status [4,55].

The intensity and duration of anticholinergic symptoms associated with BZ exposure are dose-dependent, with higher doses causing more severe symptoms and a longer duration of effect. Incapacitating symptoms typically appear within 1 hour after exposure, peak at approximately 8 hours after exposure, and subside gradually during the next 48 to 72 hours. All individuals exposed to BZ should be decontaminated by washing the entire body with soap and water. Medical therapy is mostly supportive, to include control of the patient for the prevention of accidents, removal of dangerous objects from the patient's environment to prevent self-inflicted harm during delirium, moist swabs or hard candy for dryness of the mouth, keeping the room temperature at 75°F or below to prevent the development of hyperthermia, and the use of topical antibiotics and sterile dressings for abrasions of dry, parched skin. Severe signs and symptoms of BZ exposure can be treated with physostigmine. Physostigmine temporarily raises acetylcholine concentrations by binding reversibly to anticholinesterase on postsynaptic or postjunctional membranes. Physostigmine can be administered either intravenously or intramuscularly. The recommended intravenous dose is 30 µg per kg by slow infusion at a rate of 1 mg per minute. The recommended intramuscular dose is 45 µg per kg in adults and 20 µg per kg in children. The patient should be evaluated every hour for improvement in signs and symptoms, with physostigmine readministered periodically at a dose and time interval that is titrated to the severity of clinical signs. Physostigmine can cause a precipitous decrease in heart rate and patients should be carefully monitored during its administration. It should not be administered to any patient with cardiopulmonary instability, hypoxemia, electrolyte imbalance, or acid–base disturbances that predispose to cardiac dysrhythmias and seizures. It is recommended that an intravenous test dose of 1 mg be administered to adults if the diagnosis of BZ exposure is in doubt. If slight improvement is noted and there are no adverse effects within 1 hour, the full dose can be given [4,55].

Riot control agents are intended to produce unpleasant but nonpersistent medical effects. They are sometimes referred to as

irritants. The two riot control agents most commonly used are 2-chloro-1-phenylethanone (CN or MACE; MACE Security International, Bennington, VT) and 2-chlorobenzalmalononitrile (CS or tear gas). Another product used for riot control or security is oleoresin capsaicin (OC or pepper spray). All riot control agents cause significant irritation to the eyes, upper airways, and skin. In addition to burning of the eyes and increased lacrimation, exposed individuals may experience temporary blepharospasm with transient blindness. Upper airway symptoms include rhinorrhea, sneezing, salivation, and tightness of the chest. Exposed individuals with preexisting reactive airway disease may develop bronchospasm, which can progress to respiratory failure [56]. Because riot control agents are dispersed as a solid powder, decontamination consists of getting the victims into fresh air, removing their clothing, and irrigating their eyes and mucous membranes with normal saline. Treatment is nonspecific and supportive. Most symptoms resolve in 15 to 30 minutes. Episodes of acute bronchospasm in susceptible individuals should be treated with a short-acting β_2 agonist administered by nebulizer [57].

Finally, a variety of other readily available compounds can be aerosolized and need to be considered as potential incapacitating agents. Nausea-producing agents such as diphenylaminearsine (DM or "adamsite") can produce incapacitating gastrointestinal symptoms. Psychedelic drugs, such as 3,4-methylenedioxymethamphetamine and phencyclidine, are easily obtained and could be used as aerosolized incapacitating agents. In October 2002, carfentanil, a potent aerosolized derivative of fentanyl, was probably employed in combination with halothane in an attempt by Russian authorities to release more than 800 hostages held by terrorists in Moscow's Dubrovka Theater. Unfortunately, 127 hostages in the theater died and more than 650 were hospitalized after being exposed to the chemicals that were used in the rescue attempt [58]. This is a good example of how readily available pharmaceutical agents can be used to incapacitate, or even kill, a large number of individuals.

SUMMARY

Chemical agents pose a significant threat to populations throughout the world, whether accidentally released from an industrial or transportation accident, or released intentionally as part of a crime or terrorist event. Regardless of the cause of release, they have the potential to produce a large number of casualties in a short period of time. However, the terminology *weapons of mass destruction* does not entirely reflect the impact that a terrorist attack with such agents could have on the general population. Even a relatively small number of casualties from a terrorist attack would be likely to cause significant psychological trauma, resulting in anxiety and behavioral changes among large numbers of "worried well." Such psychological trauma could significantly disrupt normal business and community activities for a long period of time. Instilling widespread fear and anxiety in the general population is a primary goal of terrorism and, unfortunately, the use of chemical agents is an efficient method of achieving that goal.

Critical care providers must be prepared to deal with the recognition, decontamination, transport, medical treatment, and psychological trauma of casualties resulting from chemical agents. They must also be prepared to protect themselves and colleagues from contamination with chemical agents during the course of patient care. Training in the medical management of chemical agent casualties and planning for mass casualty situations are essential to ensure that the best possible care is provided to the victims of a chemical exposure or chemical attack.

DECLARATION

The opinions and assertions contained herein are those of the authors and do not necessarily reflect the views or position of the Department of Veterans Affairs, Dartmouth Medical School, or the Medical University of South Carolina.

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CHAPTER 215 ■ THE MANAGEMENT OF ACUTE RADIATION CASUALTIES

LAWRENCE C. MOHR JR

INTRODUCTION

It has been stated by the nation's political and military leadership that it is not a matter of "if" but "when" another terrorist attack will occur within the continental United States. Such future attacks could include the use of a radiological dispersion device, commonly called a "dirty bomb," an attack on a nuclear power plant or the detonation of a nuclear weapon. Indeed, a nuclear attack by a group of rogue terrorists is the single greatest risk to our homeland security. The objective of this chapter is to become familiar with the medical consequences of a radiological or nuclear attack and the management of casualties that could result from such an attack. It is to help you to think about the "unthinkable."

RADIOLOGICAL WEAPONS OF TERRORISM

Radiological dispersion devices, or "dirty bombs," consist of radioactive materials that are placed around a high explosive charge. The radioactive material is released and dispersed by detonation of the high explosive charge. Dirty bombs are easy to make and raw materials are readily available throughout the world. It is important to note that dirty bombs are not nuclear weapons and are not weapons of mass destruction. Their adverse health effects depend on the type and amount of explosive used, the type and amount of radioactive material used, and atmospheric conditions at the time of detonation. Most injuries from a dirty bomb will come from the blast effects of the conventional explosion [1,2]. Acute radiation health effects are very unlikely. Delayed health effects, such as the development of cancer, are also unlikely. The risk of developing cancer following a dirty bomb attack is related to the radiation exposure dose and to the amount of internal radiation that results from the inhalation, ingestion, and absorption of radioactive material through the skin or open wounds. Long-term psychological trauma is likely to occur among some members of a population who have been exposed to radioactive material from a dirty bomb [2,3].

A nuclear explosion results from nuclear fission or from thermonuclear fusion, in which a tremendous amount of energy is suddenly released in the form of heat, blast, and radiation. Human injury is caused by exposure to a combination of these three forms of energy following a nuclear detonation. The radiation exposure from a nuclear explosion can be very intense and lead to a life-threatening acute radiation syndrome, radiation burns, thermal burns, and blast injuries. Such radiation exposure can also result in the development of various types of cancer and leukemia over a period of many years if an individual survives the short-term initial effects of a nuclear explosion [4–6].

The life-threatening acute radiation syndrome may develop in some radiation-exposed individuals following a nuclear explosion. The acute radiation syndrome consists of a continuum of complex and unique medical sub-syndromes that involve the hematopoietic, gastrointestinal, and central nervous systems in a dose-related fashion. Patients who develop any of the acute radiation sub-syndromes require prompt assessment and critical care management in order to minimize loss of life. It is essential that any physician who may be called upon to treat patients following a nuclear explosion be familiar with the diagnosis and management of these unique sub-syndromes [7]. The acute radiation syndrome and its associated sub-syndromes are discussed in detail later in the chapter.

BASIC RADIATION PHYSICS

In order to understand the medical aspects of radiation exposure, it is important to review some basic principles of radiation physics. *Radiation* is defined, simply, as energy that is transmitted through space. The transmitted energy may be in the form of high-speed particles or electromagnetic waves. There are two general types of radiation: ionizing radiation and nonionizing radiation. Ionizing radiation has enough energy, so that when it interacts with an atom, it can remove tightly bound electrons from their orbits and cause the atom to become charged. Nonionizing radiation, on the other hand, does not have enough energy to remove electrons from their orbits. Ionizing radiation is more harmful to humans than nonionizing radiation and is the type of radiation that would be expected to be released in a radiological or nuclear attack.

Ionizing radiation can take four forms: alpha, beta, gamma, and neutron radiation. Alpha radiation consists of the emission of a helium nucleus from a parent nucleus, such as ^{235}Uranium; it is a particle that has an atomic mass of four and a charge of plus one. Beta radiation is the emission of a small negatively charged particle from a parent nucleus, such as ^{40}Potassium. Beta particles have a mass that is almost undetectable and a charge of minus one, similar to that of an electron. Gamma radiation is the emission of high-energy electromagnetic waves from a parent nucleus, such as ^{60}Cobalt. Gamma rays have no mass, no charge, and frequently accompany the emission of alpha or beta particles. Neutrons are very high-energy particles that are emitted from parent nuclei, such as ^{235}Uranium and ^{239}Plutonium during a nuclear chain reaction. Nuclear chain reactions can be controlled, such as the kind found in a nuclear reactor, or they can be uncontrolled, such as the type that causes a nuclear explosion. Neutrons are very damaging to human cells and tissues [8,9].

Each specific type of ionizing radiation has a different penetrating distance with respect to inert material and human tissues. Alpha particles will not penetrate paper or human skin. Indeed, you can safely hold an alpha-emitter, such as ^{240}Plutonium, in your hand as long as you do not have any breaks in the skin. However, if alpha particles are ingested, inhaled, or internalized through a break in the skin, they can do

a tremendous amount of internal damage to human cells and tissues [8,9].

Beta radiation will penetrate paper, thin layers of skin, and the conjunctiva of the eye, but will not penetrate thin layers of plastic or aluminum foil. Beta particles travel relatively short distances and will be stopped by most clothing. As with alpha particles, beta radiation is more damaging to human tissues if inhaled or ingested [8,9].

Gamma rays can travel significant distances and are a highly penetrating type of ionizing radiation. They readily penetrate skin and clothing. Gamma radiation can cause considerable damage to human cells and tissues after penetration. Several inches of lead or several feet of concrete are required to stop gamma rays [8,9].

Neutrons are high-energy nuclear particles that have no charge. Neutron radiation easily penetrates skin and clothing and can cause significant damage to internal tissues and organs. Neutrons primarily cause biological damage by colliding with other particles. They transfer the most energy when they collide with particles that are about the same size, especially protons. These high-energy, subatomic collisions result in the dislodgement of both protons and tightly bound electrons from atoms that are bombarded by neutrons, with ionization of atoms in surrounding cells and tissues. Neutron radiation is extremely harmful to humans. It is not stopped by plastic, glass, or lead; it can only be stopped by several feet of concrete [8,9].

Ionizing radiation causes damage to human cells and tissues through two biological mechanisms: (i) direct high-energy damage to DNA molecules and (ii) the generation of free radicals, which secondarily damage DNA molecules by superoxide radicals generated from ionized water. The fate of irradiated human cells is dependent on the dose of radiation exposure. Low-dose exposures are characterized by DNA and cellular repair. Moderate-dose exposures are characterized by permanently damaged DNA and significantly altered cells, which may be eliminated by apoptosis, or reproduce abnormally and eventually lead to the development of cancer. High-dose radiation exposures typically result in cell death, which causes several serious, acute radiation syndromes that can result in death of the organism [10,11].

Human radiation exposure can be categorized as either external or internal. External exposure, which involves exposure to the skin, may be either whole body or partial body depending on the surface area exposed to radiation. Internal exposure may occur from the inhalation, ingestion, or transdermal penetration of radioactive material. Combined radiation injuries may also occur in cases where radiation exposure and trauma occur concurrently. In combined radiation injuries, radioactive material is introduced through open wounds [8].

RADIATION DOSES

There are two units of radiation dose that physicians must be familiar with: the Rad and the Gray. It is not essential for physicians to understand the physics that underlie the determination of these doses, but it is important for them to know that these are the units which are used to express the amount of radiation that is absorbed by human tissues. The Rad is the traditional unit of **r**adiation **a**bsorbed **d**ose. One Rad is defined as 100 ergs per g. The Gray (abbreviated Gy) is the newer Standard International unit of radiation exposure. One Gy is equal to 100 Rads, which is defined as 1 J per kg. One hundred centi-Gray (100 cGy) are equal to 1 Gray [12].

Radiation doses can be measured by several techniques. A radiac meter is an instrument that directly measures radiation dose using a Geiger–Müller tube or similar device. There are many different types of radiac meters, each of which may be more sensitive to specific types of radiation, such as alpha, gamma, or neutrons, than to other types of radiation. It is important, therefore, to know both the capabilities and limitations of any radiac meter that one uses to determine radiation doses. Most radiac meters in use today are highly portable and will accurately measure alpha, beta, gamma, and neutron radiation. The measurement of the lymphocyte count between 24 and 48 hours after exposure can provide a useful biological estimate of radiation dose, especially in the clinical setting [13]. The dose range in Gy and the estimated lethality associated with each dose range is illustrated in Table 215.1.

TABLE 215.1

LYMPHOCYTE COUNT BETWEEN 24 AND 48 HOURS AFTER RADIATION EXPOSURE, ESTIMATED DOSE RANGE (Gy), AND ESTIMATED LETHALITY (%)

Lymphocyte count (× 1,000/mm^2)	Dose range (Gy)	Lethality (%)
3.0	0–0.25	—
1.2–2.0	1–2	< 5
0.4–1.2	2.0–3.5	< 50
0.1–0.4	3.5–5.5	50–99
0–0.1	> 5.5	99–100

From Walden TL, Farzaneh MS. Biological assessment of radiation damage, in Walker RI,, Cerveny TJ (eds): *Medical Consequences of Nuclear Warfare,* in Zajtchuk R Bellamy RF (eds): *Textbook of Military Medicine, Part I: Warfare, Weaponry and the Casualty*. Washington, *DC, United States Department of the Army, Office of the Surgeon General and Borden Institute*, 1996, p 87. Available at: http://www.usuhs.mil/afrri/outreach/pdf/tmm/chapter6/chapter6.pdf.

Chromosomal aberrations and translocations in lymphocytes can provide a useful estimate of both the type of radiation that one has been exposed to as well as the radiation dose [14]. This method requires considerable expertise in fluorescent in situ hybridization techniques as well as expertise in the interpretation of the chromosomal abnormalities. As a result, the analysis of chromosomal aberrations is primarily used as a research tool at the present time.

OVERVIEW OF RADIATION CASUALTIES

Radiation casualties consist of two general types: an acute radiation syndrome and delayed illnesses that may occur many years after radiation exposure. Acute radiation syndrome is a life-threatening condition consisting of a continuum of dose-related sub-syndromes that occur shortly after a high-dose radiation exposure, such as may occur following the detonation of a nuclear weapon. Delayed illnesses include leukemia, lymphoma, and various solid tumors, which may occur later in life following radiation exposure doses that are lower than those needed to produce acute radiation illness. In general, the higher the radiation dose, the more severe the acute effects of radiation exposure, the greater the probability of delayed illnesses, and the higher the mortality rate [4,7,15].

In considering the human dose-response to radiation exposure, a measurement known as the $LD_{50/60}$ is commonly used. The $LD_{50/60}$ is the radiation dose that causes a 50% mortality rate in an exposed population within 60 days following exposure. For whole-body radiation exposure, the $LD_{50/60}$, with no treatment, is 3 to 4 Gy. Therefore, 50% of a population that receives a radiation dose of 3 to 4 Gy will die within 60 days unless they receive treatment. With appropriate treatment and

supportive care following radiation exposure, the $LD_{50/60}$ is 4 to 5 Gy [7,12].

ACUTE RADIATION SYNDROME AND SUB-SYNDROMES

Acute radiation syndrome is a continuum of dose-related organ system sub-syndromes that develop after an acute radiation exposure of greater than 1 Gy. There are three main sub-syndromes that occur: the hematopoietic sub-syndrome, the gastrointestinal sub-syndrome, and the central nervous system sub-syndrome. Each of these sub-syndromes occurs in a dose-related fashion. The hematopoietic sub-syndrome occurs with radiation exposures greater than 1 Gy. The gastrointestinal sub-syndrome occurs in addition to the hematopoietic sub-syndrome at radiation exposures greater than 6 Gy. The central nervous system sub-syndrome occurs in addition to the hematopoietic and gastrointestinal sub-syndromes at radiation exposures greater than or equal to 20 Gy.

All acute radiation sub-syndromes begin with a *prodromal phase* that lasts for 2 to 6 days. This phase is characterized by nausea, vomiting diarrhea, and fatigue. The higher the radiation dose, the more rapid the onset, and the more severe the symptoms of the prodromal phase. After 2 to 6 days of the prodromal phase, the patient enters a *latent phase*, in which he or she appears to recover and is totally asymptomatic. The latent phase lasts for several days to 1 month, with the time period inversely proportional to the radiation exposure dose, that is, the higher the dose, the shorter the latent period. After the asymptomatic latent period, the patient enters the *manifest illness phase*. This phase of acute radiation illness lasts from several days to several weeks and is characterized by the manifestation of the hematopoietic, gastrointestinal, and central nervous system sub-syndromes, according to the exposure dose that the patient received [16].

Some individuals may develop a radiation-associated multiple organ dysfunction syndrome in association with the organ-specific clinical syndromes mentioned in the previous paragraph. Multiple organ system dysfunction typically occurs in the manifest illness phase, but may also occur early after a sublethal radiation exposure. Patients with hematopoietic, gastrointestinal, central nervous system, and multiple organ dysfunction syndromes will require management in an intensive care unit [17,18].

The Hematopoietic Sub-Syndrome

The hematopoietic sub-syndrome typically occurs with a radiation dose of greater than 1 Gy. It is characterized by bone marrow suppression resulting from the radiation-induced destruction of hematopoietic stems cells within the bone marrow. Hematopoietic stem cell destruction results in pancytopenia, which is characterized by a progressive decrease in lymphocytes, neutrophils, and platelets in the peripheral blood. Both the magnitude and the time course of the pancytopenia are related to the radiation dose. In general, the higher the radiation dose, the more profound and the quicker the pancytopenia occurs [7,16].

Lymphocytic stem cells are exquisitely sensitive to radiation and circulating lymphocytes decrease rapidly following radiation exposure and remain low for a long period of time. Erythrocytic stem cells, on the other hand, seem to be more resistant to radiation than lymphocytic, neutrophilic, and thrombocytic stem cells. Therefore, the red blood cell count and hemoglobin concentration typically do not decrease to the same extent as lymphocytes, neutrophils, and platelets following radiation exposure. Hematological effects that occur in the manifest illness phase of the hematopoietic sub-syndrome following radiation exposures of 1 Gy and 3 Gy are depicted in Figure 215.1.

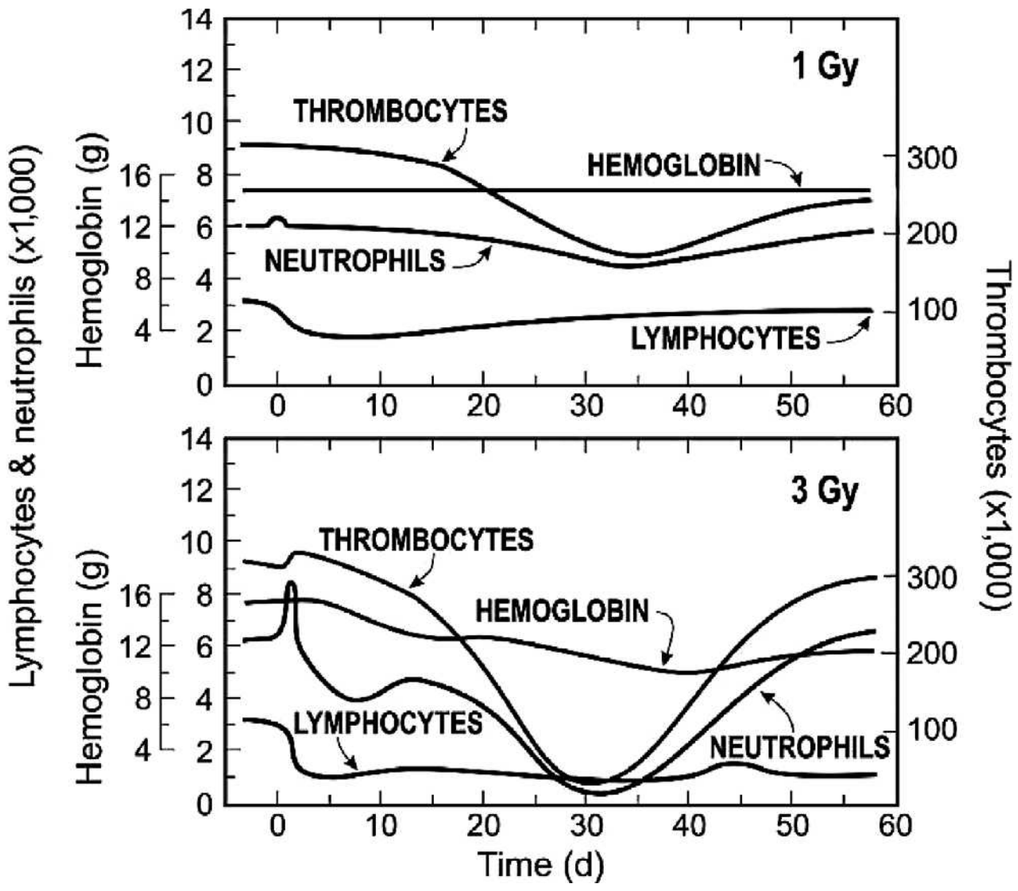

FIGURE 215.1. Hematological effects in the manifest illness phase of the hematopoietic sub-syndrome following radiation exposures of 1 and 3 Gy, respectively. [From Cerveny TJ, McVitte TJ, Young RW: Acute radiation syndrome in humans, in Walker RI, Cerveny TJ (eds): *Medical Consequences of Nuclear Warfare*, in Zajtchuk R, Bellamy RF (eds): *Textbook of Military Medicine, Part I: Warfare, Weaponry and the Casualty*. Washington, DC, United States Department of the Army, Office of the Surgeon General and Borden Institute, 1996, p 19. Available at: http://www.usuhs.mil/afrri/outreach/pdf/tmm/chapter2/chapter2.pdf. Accessed April 14, 2010.

As seen in Figure 215.1, the hematological effects of acute radiation exposure are dependent on the radiation dose. A radiation exposure of 3 Gy or more results in significant hematological effects than a radiation exposure of 1 Gy. Lymphocytes will decrease very rapidly following a radiation exposure of 3 Gy, and they will stay low for a relatively long period of time. Typically, it takes about 90 days before lymphocytes begin to recover from a 3 Gy radiation exposure. Neutrophils, after an initial period of intravascular demargination, will also begin to decline fairly rapidly following a 3 Gy exposure. Neutrophils do not fall as rapidly as lymphocytes, but between 3 and 5 days following exposure, such patients will be significantly neutropenic. Platelets also decrease steadily following a 3 Gy exposure and patients will become significantly thrombocytopenic at 2 to 3 weeks. Both platelets and neutrophils will reach a nadir, with values close to zero, at about 30 days following a 3 Gy exposure. Platelets and neutrophils then recover gradually during the next 30 days. Lymphocytes remain low for a long period of time, however, and typically do not begin to recover for at least 90 days following a 3 Gy exposure. Thus, there is a period of about a month following a 3 Gy exposure when patients will be significantly lymphopenic, neutropenic, and thrombocytopenic. Such patients are susceptible to developing serious infections and serious bleeding problems during that time [7].

The Gastrointestinal Sub-Syndrome

The gastrointestinal sub-syndrome typically occurs following a radiation dose of greater than 6 Gy. It develops as a result of radiation damage to intestinal epithelial cells. The loss of

epithelial cells results in denudation of the intestinal mucosa. Following the asymptomatic latent phase, patients will develop a manifest illness phase characterized by fever, vomiting, and severe diarrhea. Malabsorption, severe fluid losses, and severe electrolyte derangements will follow. Most patients will have severe pancytopenia as a result of a coexisting hematopoietic sub-syndrome. Sepsis and opportunistic infections commonly occur. The resulting sepsis can be very severe, and typically involves enteric organisms that migrate into the systemic circulation through damaged and denuded gastrointestinal mucosa. Approximately 10 days after the onset of the manifest illness phase, these patients typically develop fulminate bloody diarrhea that usually results in shock and subsequent death [7,16,19].

The Central Nervous System Sub-Syndrome

The central nervous system sub-syndrome is seen with radiation doses greater than or equal to 20 Gy, although cognitive dysfunction can be seen with radiation doses greater than 10 Gy. The latent period is very short, lasting from several hours to 3 days. Following the asymptomatic latent period, patients typically develop nausea, vomiting, diarrhea, and confusion. Microvascular leaks in the cerebral circulation result in cerebral edema. Elevated intracranial pressure and cerebral anoxia may develop rapidly. Mental status changes develop early in the manifest illness phase and the patient eventually becomes comatose. Seizures and burning dysesthesia may occur. Patients typically die within hours after onset of the manifest illness phase of the central nervous system sub-syndrome [1,7,20,21].

Multiple Organ Dysfunction Syndrome

As mentioned previously, some patients may develop multiple organ system dysfunction following exposure to ionizing radiation. This was first reported following a 1999 nuclear accident in Japan [22–24]. Idiopathic pneumonia syndrome, acute respiratory distress syndrome, diffuse alveolar hemorrhage, fluid and electrolyte abnormalities, bacteremia, and acute renal insufficiency may occur [17]. The specific causes of radiation-associated multiple organ system dysfunction are unknown. Similarly, there is no well-defined dose–effect relationship that has been associated with its development. However, there are several clues to possible pathogenic mechanisms. It is known that whole body radiation exposure causes severe inflammation, which is probably mediated by the generation of reactive oxygen species and cytokines [25–27]. Increased permeability of blood vessels has also been observed shortly after radiation exposure [22,25]. Furthermore, hemorrhagic shock, the inability to increase oxygen consumption with adequate oxygen delivery, and sepsis, all of which may occur following radiation exposure, have been associated with multiple organ system dysfunction [25,28,29]. From a clinical perspective, it is important to understand that all of these phenomena may contribute to the unpredictable and rapid development of multiple organ system dysfunction in some patients following acute radiation exposure. Such patients will require prompt supportive care and treatment in an intensive care unit in order to maximize the potential for survival [17].

Prognosis

The prognosis of patients who develop acute radiation sub-syndromes depends on the radiation dose to which they were acutely exposed. Patients who are exposed to 1 to 2 Gy will probably survive. Survival is possible in patients who are exposed to doses of 2 to 5.5 Gy, but many of these patients will require prompt treatment and intensive care in order to survive. Survival is possible, but improbable, in patients who are exposed to doses of 5.5 to 10 Gy. Even with the most aggressive treatment, survival is extremely rare following exposure doses above 10 Gy and impossible following doses greater than 20 Gy [30].

Management

All patients should receive basic supportive care following acute radiation exposure. This consists of fluid and electrolyte balance, antiemetic agents to manage vomiting, antidiarrheal agents to manage diarrhea, proton pump inhibitors for gastrointestinal ulcer prophylaxis, pain management, psychological support, and pastoral care if death is likely. In patients with any of the acute radiation sub-syndromes, it is important not to instrument the gastrointestinal tract, since this could result in perforations that precipitate fulminate bleeding or sepsis [31,32].

Cytokine therapy with a colony-stimulating factor should be given to certain patients in order to stimulate neutrophil production in the bone marrow [30]. If there are less than 100 casualties, cytokines should be given to patients with no other injuries who have had a radiation exposure of 3 to 10 Gy. If patients in this category have multiple injuries or burns, they should receive cytokine therapy if they received a radiation dose of 2 to 6 Gy. If, on the other hand, the number of casualties is greater than 100, cytokines should be given to patients with no other injuries who have had a radiation exposure dose of 3 to 7 Gy and to patients with multiple injuries or burns who have had an exposure dose of 2 to 6 Gy [30–32].

Various types of granulocyte colony-stimulating factor (G-CSF) can be given: G-CSF (Filgrastim), pegylated G-CSF (Pegfilgrastim), or GM-CSF (Sargramostim). These are all commercially available preparations and they are all effective. The recommended doses of the various cytokines for the treatment of acute radiation sub-syndromes in adults are summarized in Table 215.2.

There are also guidelines for the use of antibiotics following acute radiation exposure [26–28]. If the total number of casualties is 100 or less, patients with no other injuries should be given antibiotics if they have been exposed to a radiation dose of 2 to 10 Gy. Patients in this category with multiple injuries or burns should be given antibiotics if they have received a radiation exposure dose of 2 to 6 Gy. In a mass casualty situation, in which there are more than 100 casualties, patients with no other injuries should be given antibiotics if they received a radiation exposure of 2 to 7 Gy. Patients in a mass casualty situation who have multiple injuries or burns should be given antibiotics if they received a radiation exposure dose of 2 to 6 Gy [30–32].

The specific antibiotic regimen used in the management of an acute radiation sub-syndrome should depend on the antibiotic susceptibilities of any specific organisms that are able to be isolated from blood or tissue cultures. It is generally recommended that a fluoroquinolone with streptococcal coverage be used, along with acyclovir or one of its congeners for viral coverage, and fluconazole for the coverage of fungi and candida. Once culture results are obtained, specific antibiotic treatment should be given according to the sensitivities of any organisms that are isolated. Antibiotics should be continued until the absolute neutrophil count is greater than 0.5×10^9 cells per L, until they are no longer effective, or for the duration indicated for specific organisms that have been isolated [30–32].

Blood transfusions are indicated for patients with an acute radiation sub-syndrome who have severe bone marrow damage or who require concurrent trauma resuscitation. The purpose

TABLE 215.2

RECOMMENDED DOSES OF CYTOKINES

Cytokine	Adults	Children	Pregnant women[a]	Precautions
G-CSF or filgrastim	Subcutaneous administration of 5 µg/kg of body weight per day, continued until ANC > 1.0×10^2 cells/L	Subcutaneous administration of 5 µg/kg/d, continued until ANC > 1.0×10^2 cells/L	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS; consider discontinuation if pulmonary infiltrates develop at neutrophil recovery
Pegylated G-CSF or pegfilgrastim	1 subcutaneous dose, 6 mg	For adolesoents > 45 kg, 1 subcutaneous dose, 6 mg	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS
GM-CSF or sargramostim	Subcutaneous administration of 250 µg/m^2/d, continued until ANC > 1.0×10^2 cells/L	Subcutaneous administration of 250 µg/m^2/d, continued until ANC > 1.0×10^2 cells/L	Class C (same as adults)	Sickle-cell hemoglobinopathies, significant coronary artery disease, ARDS; consider discontinuation if pulmonary infiltrates develop at neutrophil recovery

[a]Express in biodosimetry must be consulted. Any pregnant patient with exposure to radiation should be evaluated by a health physicist and maternal-fetal specialist for an assessment of risk to the fetus. Class C refers to U.S. Food and Drug Administration Pregnancy Category C which indicates that studies have shown animal, terarogenic, or embryocidal effects, but there are no adeqate controlled studies in women; or no studies are available in animals or pregnant women.
ANC, absolute neutrophil count; ARDS, acute respiratory distress syndrome; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

of blood transfusions in such patients is to provide erythrocytes for the improvement of oxygen-carrying capacity, blood volume to improve hemodynamic parameters, and platelets to help prevent bleeding. Cytokines, not blood transfusions, are used to increase absolute neutrophil counts, according to the criteria and doses previously discussed. All cellular products in the blood to be transfused should be leukoreduced and irradiated to 25 Gy in order to prevent a graft versus host reaction. Leukoreduction also helps to protect against platelet alloimmunization and the development of cytomegalovirus infections [17,30].

Stem cell bone marrow transplantation should be considered for certain patients with acute radiation illness. Allogenic stem cell transplantation is indicated for individuals who have a radiation exposure dose of 7 to 10 Gy. If a patient is fortunate enough to have a stored autograft bone marrow specimen or a syngenetic donor, preferably an identical twin, stem cell transplantation should be considered if they have had radiation exposure doses of 4 to 10 Gy [30,31].

ACUTE RADIATION ILLNESS AND TRAUMA

The blast from a nuclear detonation can produce powerful, high-pressure winds that have greater velocities than the most powerful hurricane winds. These winds can extend miles from the point of detonation. They can cause large numbers of seriously injured casualties from missiles caused by flying debris or from individuals being blown against objects in the environment.

The combination of an acute radiation syndrome and trauma presents some special challenges to the physician. There is a significant increase in mortality among patients who have this combination of illness and injury and such patients require prompt medical and surgical care in order to survive. They should receive the standard treatment for acute radiation syndromes, as described earlier. They are also very susceptible to operative and postoperative infections as a result of decreased neutrophil and lymphocyte counts and require 2 to 3 months for the bone marrow to recover after acute radiation exposure. This greatly complicates the management of such patients, especially those with multiple, serious injuries. Most importantly, if a patient with a combination of an acute radiation syndrome and trauma requires surgery, the operation should be performed within 48 hours after the initial radiation exposure. If surgery is not performed in this "window of opportunity" following acute radiation exposure, it may have to be postponed for up to 2 to 3 months [31,33]. Therefore, all radiation-exposed patients with life-threatening traumatic injuries should be transported to a surgical care facility and receive emergency surgery as soon as possible within the 48-hour "window."

ACUTE RADIATION DERMATITIS

An acute radiation dermatitis may occur in conjunction with acute radiation illness. The symptoms and signs of acute radiation dermatitis typically appear several days *after* an acute radiation exposure. Although acute radiation dermatitis is essentially a radiation burn, it is different from the thermal burns that may occur *immediately* after exposure of the skin to a nuclear explosion. In this regard, radiation burns and thermal burns are different. Exposure of the skin to radiation causes loss of the epidermal layer at radiation doses greater than 2 Gy. This leads to erythema and blisters. Loss of the dermis occurs at radiation exposure doses of greater than 10 Gy, and this results in the development of skin ulcers. Skin ulcerations that result from radiation doses greater than 10 Gy heal very slowly over a period of many months, if they heal at all. Chronic skin ulcers in patients with acute radiation illness predispose these patients to the development of serious infections. Such ulcers should be debrided early in their development to help prevent infection. Topical antibiotics, such as mafenide acetate or silver sulfadiazine, should be applied prophylactically. However, since these topical antibiotics can cause neutropenia, they should be used judiciously with careful monitoring of the absolute

neutrophil count in severely neutropenic patients. Although no studies have been conducted on the efficacy of skin grafting in radiation burn patients, it is recommended that an attempt should be made to graft full-thickness burns and ulcers [33,34].

INTERNAL CONTAMINATION

In the assessment of patients with acute radiation exposure, it is important to ascertain whether or not they have experienced any internal contamination. Internal radiation contamination can occur by the inhalation, ingestion, or the transdermal penetration of radioactive material. It can occur via a variety of portals, such as the nose, the mouth, a wound, or, with a large enough dose, by the penetration of gamma rays or neutrons directly through intact skin. Internal organs commonly affected by internal radiation contamination are the thyroid, the lung, the liver, adipose tissue, and bone. These are the areas where radioactive isotopes tend to accumulate within the human body. Leukemia and various types of cancers can develop in these organs many years after an acute radiation exposure with internal contamination.

Assessment of Potential Internal Radiation Contamination

The patient history is crucial to determining whether or not they may have experienced internal contamination. Any history which suggests that a patient may have inhaled, ingested, or internalized radioactive material through open wounds should prompt further evaluation for internal contamination. This assessment should attempt to identify both the radiation dose received and, if possible, the specific isotopes that cause the internal contamination. An initial survey of the patient should be performed with a radiac meter, especially around the mouth, nose, and wounds, to give some idea of the extent of any possible internal exposure. The diction of radioactive isotopes on nasal swabs can be very helpful to determine whether or not a patient has been exposed internally. If it is suspected that a person has inhaled a significant amount of radioactive material, bronchoalveolar lavage can be considered for the purposes of identifying inhaled radioactive isotopes as well as for removing residual radioisotopes from the lungs. Bronchoalveolar lavage has been shown to be effective in removing inhaled radioactive isotopes from the lungs of animals. The collection of stool and urine samples can be very helpful in determining both the type and the amount of internal radiation that an individual might have received. Chest and whole-body radiation counts can also be helpful in determining the extent of any internal radiation contamination. Unfortunately, however, most medical institutions do not have the capability to do either chest or whole-body radiation counts. The analysis of nasal swabs, stool samples, and urine samples are the most practical methods of determining the type and extent of internal radiation contamination by hospital-based physicians [35,36].

Treatment of Internal Radiation Contamination

Patients who have experienced internal radiation contamination should be promptly treated in order to reduce the absorbed radiation dose and prevent the development of future health problems. The goals of treatment are to reduce absorption and enhance elimination of the internal radionuclide contaminant. There are three main categories of agents that are used to treat internal radiation contamination: purgative agents, blocking agents, and chelation agents. Specific agents are used to treat internal contamination by specific radioactive isotopes. Such treatment is most effective when given as soon as possible after the radiation exposure. Gastric lavage can be used to empty the stomach completely after the potential ingestion of radionuclides. If promptly performed, it could decrease the concentration of radionuclides in the gastrointestinal tract. This could result in a decrease of the absorbed radiation dose. In deciding whether or not to treat a patient for internal radiation contamination, the physician may need to act on preliminary information and may have to treat potentially exposed individuals empirically, based on the information that is available [35,36].

Purgative Agents

Purgative agents help to remove radionuclides from the gastrointestinal tract. The most common purgatives are laxatives and enemas, which are helpful in reducing the residence time of radionuclides in the colon. Prussian blue (ferric ferrocyanide) is an ion exchange resin that binds ^{137}cesium in the gastrointestinal tract and facilitates its secretion. Patients who have experienced internal ^{137}cesium contaminate should be treated with oral Prussian blue (3 g, three times daily) for at least 3 weeks. Aluminum phosphate binds ^{90}strontium in the gastrointestinal tract. A single, 100 mL oral dose of aluminum phosphate gel will reduce the gastrointestinal absorption of ^{90}strontium by 85%. Oral aluminum phosphate should be used if internal contamination with ^{90}strontium is expected [35,36].

Blocking Agents

Blocking agents block both the uptake and bioavailability of internal radionuclide contaminants. The most important blocking agent is potassium iodide, which is used for the treatment of internal contamination with $^{125/131}$iodine. Potassium iodide blocks the uptake of radioactive iodine by increasing the uptake of nonradioactive isotope. Since the thyroid gland is very sensitive to the effects of internal contamination with $^{125/131}$iodine, potassium iodine should be given as soon as possible after radioactive iodine exposure. It is recommended that patients take 300 mg of potassium iodide per day for 7 to 14 days following a potential $^{125/131}$iodine exposure. Potassium iodide can also be taken prophylactically if there is sufficient warning of a potential $^{125/131}$iodine exposure. The standard prophylactic regimen is a single 130 mg dose of potassium iodide [35,36].

Chelation Agents

Chelation agents are the mainstay of treatment for internal radiation contamination. Chelation agents are substances that bind strongly with certain metals to form a stable, soluble complex that can be excreted by the kidneys. Diethylenetriaminepentaacetic acid (DTPA) is the most effective and commonly recommended chelation agent for the treatment of internal radiation contamination. DTPA complexes are very stable and water soluble and are unlikely to release bound radionuclides prior to renal excretion. DTPA chelation therapy is especially effective for the treatment of internal radiation contamination with ^{241}americium, ^{60}cobalt, and ^{239}plutonium. DTPA is administered as an intravenous solution of 1 g dissolved in 250 mL of saline or 5% glucose, infused over 1 hour per day for up to 5 days. DTPA can be used for the treatment of all internal radiation contaminants except $^{238-235}$uranium. The use of DTPA is contraindicated for treatment of $^{238-235}$uranium contamination because of an increased risk of renal damage. It is

TABLE 215.3

AGENTS USED TO TREAT COMMON INTERNAL RADIATION CONTAMINANTS

Radionuclide	Primary toxicity	Treatment	Agent category	Route
^{241}Americium	Bone, liver	DTPA	Chelation	IV infusion
^{137}Cesium	Total body	Prussian blue	Purgative	Oral
^{60}Cobalt	Total body	DTPA	Chelation	IV infusion
$^{125/131}$Iodine	Thyroid	Potassium iodide blocking	Oral	
^{239}Plutonium	Bone, lung	DTPA	Chelation	IV infusion
^{210}Polonium	Lung, kidney	Dimercaprol	Chelation	IM injection
^{90}Strontium	Bone	Aluminum phosphate	Purgative	Oral
$^{238-235}$Uranium	Kidney	$NaHCO_3$ and diuretic	Chelation	Oral

recommended that internal contamination with $^{238-235}$uranium be treated with oral sodium bicarbonate, with the dose regulated to maintain an alkaline urine pH. Excretion of $^{238-235}$uranium can be enhanced with the addition of a diuretic, such as furosemide [35,36].

Dimercaprol is a chelation agent that is particularly useful for the treatment of internal contamination with ^{210}polonium. Dimercaprol has been used for many years as an effective chelation agent for mercury poisoning. For ^{210}polonium contamination, 5 mg per kg of dimercaprol should be given initially, followed by 2.5 mg per kg two times daily for 10 days. Dimercaprol should be given by deep intramuscular injection only; it should not be given intravenously. Dimercaprol is very nephrotoxic and should always be used with caution. It is recommended that oral sodium bicarbonate be given to maintain an alkaline urine pH, which decreases the risk of nephrotoxicity by preventing the dissociation of the dimercaprol-^{210}polonium complex in the urine. Serum creatinine and urine pH should be carefully monitored during treatment with dimercaprol [35,36].

Need for Rapid Treatment

In order to be most effective, treatment for internal contamination should begin within hours after the radiation exposure. Early information on the history of a radiation exposure incident may or may not identify the major isotopes involved. Patients will likely present with no clinical symptoms other than conventional trauma. Therefore, critical decisions regarding the initial, empirical treatment of potential internal radiation contamination may have to be based on the historical information that is provided. It is imperative that physicians who could be involved in the management of radiation casualties be familiar with the agents used for treatment of the most likely internal radiation contaminants. These agents are summarized in Table 215.3.

DECONTAMINATION

In order to prevent contamination of other patients and medical staff, radiation casualties must be decontaminated prior to admission to a hospital. However, life-saving emergency medical care should be performed as soon as possible and before decontamination takes place. Therefore, a special emergency treatment area, where potentially contaminated patients can be treated and stabilized, will have to be set up outside the hospital. Once a patient has been stabilized, decontamination can occur in another specially designated area that is also outside the hospital. It is recommended that the designated decontamination area be at least 50 yards downwind from the hospital or other treatment area.

All healthcare workers should protect themselves with scrubs, gowns, masks, double gloves, and shoe covers during the treatment and decontamination of radiation casualties. These measures provide sufficient protection from any radioactive isotopes that could be contaminating a patient. It is recommended that healthcare workers continue to observe these measures after decontamination of a radiation casualty, since it is possible that the decontamination could be incomplete and residual radioactive material could remain on the patient. Similarly, it is best to assume that every patient in close proximity to a radiation-exposure event is contaminated, even if no radiation is detected by a radiac meter. Such patients should be decontaminated as usual and members of the decontamination team and medical treatment staff should wear protective clothing.

The decontamination process is quite simple. All of the patient's clothing must be removed and discarded into a clearly labeled and secure container, so that it does not further contaminate people and surroundings after removal. If the clothing needs to be cut off the patient, the scissors should be washed with soap and water between each cut to avoid spreading contamination on subsequent cuts. After all clothing has been removed, the patient is thoroughly washed with soap and water. This simple soap-and-water process has been shown to be effective in removing more than 95% of residual radioactive material from radiation-exposed patients [37].

Once a radiation-exposed patient has been stabilized and decontaminated, he or she should be admitted to the hospital or other treatment facility for definitive care. Again, it is best to assume that hospitalized radiation-exposed patients may still be contaminated, even after the decontamination process has been completed. Thus, it is recommended that all radiation casualties be admitted to specially designated areas of the hospital and that the staff in these areas wear appropriate protective clothing, as described earlier.

Patients exposed to potentially life-threatening doses of radiation will require critical care management during the manifest illness phase of an acute radiation sub-syndrome. In order to reduce the potential of radioactive contamination, it is recommended that such patients be cared for in specially designated areas of intensive care units or in a designated hospital area that has been converted to an intensive care unit for the management of radiation casualties.

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CHAPTER 216 ■ PLANNING AND ORGANIZATION FOR EMERGENCY MASS CRITICAL CARE

JAMES GEILING, ROBERT M. GOUGELET AND LAWRENCE C. MOHR JR

HOSPITAL AND COMMUNITY DISASTER RESPONSE

The Importance of Hospitals in Disaster Response

Hospitals and their critical care units play important roles in a community's response to a disaster, whether the disaster is sudden in nature, such as an explosion, or a more prolonged event, such as pandemic influenza. First of all, hospitals are the major source of a community's medical care and provide rapid access to health care. Most likely, the first response of an individual with a disaster-related medical problem will be to go to the closest hospital. Similarly, emergency medical system ambulances will routinely transport critically ill or injured patients to the nearest hospital. Second, hospitals are capable of managing critically ill or injured patients in a timely manner if adequate staff and resources are available. Third, it is especially difficult to provide critical care outside of the hospital setting during a disaster. For example, it may be possible to provide medical care in a building of opportunity, such as a school gymnasium, for low-acuity patients. However, providing critical care in such a setting would require significant amounts of medical equipment, supplies, and specially trained staff. It would be logistically difficult, costly, and time consuming to move critical care resources to a nonhospital facility during a disaster. Finally, hospitals which are accredited by the Joint Commission or other accrediting agencies must meet specific requirements for disaster preparedness. These requirements include continuity-of-operations plans, an internal operations center with an incident command structure, and the planning and conduct of disaster response exercises in coordination with the neighboring community.

In summary, the hospital is the major healthcare asset in disaster response and is likely to be the only facility where critical care is provided. In order to maintain its capability to respond to the most critical patients during a disaster, the hospital must be part of a community-based healthcare response system that can be efficiently mobilized during a catastrophic event.

The large numbers of patients requiring care immediately after a disaster, the continued flow of patients during a prolonged disaster, or the loss of hospital infrastructure as a result of a disaster, all have the potential to overwhelm available resources at any hospital. Thus, it is possible that there will be limits to the number of patients that can be cared for and the level of care that can be provided by a hospital during a catastrophic event.

Surge capacity generally refers to the ability to manage a sudden or prolonged increase in numbers of patients that would otherwise severely challenge or exceed the present capacity of the facility. Medical surge capacity may be defined, more technically, as "the quantifiable amount of community or regional resources and services available for providing medical care in emergencies that overwhelm the normal medical infrastructure" [1]. To provide adequate surge capacity and maintain medical system resiliency during disasters, hospitals and communities must have medical preparedness plans, as well as carefully planned command and control systems that will efficiently manage the medical response.

Local Community Medical Response

Incident Command Systems

In the United States, both hospitals and community governments are required to adhere to the requirements of the National Incident Management System, which is managed by the Federal Emergency Management Agency [2]. This includes the requirement that both hospitals and communities have an Incident Command System (ICS) [3]. The currently used ICS model for disaster response is a modular system that follows the basic principles of organizational leadership, with one person in charge of a command section that supervises the activities of 3 to 7 subsections. Most ICS structures have five principal components:

1. *Leadership*—This is the command section, chaired by the leader of the response effort (the incident commander). The incident commander is supported by special staff, such as public affairs, public safety, legal counsel, etc.
2. *Operations*—This section oversees and coordinates the immediate response and ongoing operational activities. This tends to be the most active section during a disaster.
3. *Planning*—This section assesses the potential for future events, develops contingency plans for future events, and plans timelines for the deployment of critical resources. These planning activities permit the operations branch to focus on managing the response to active events.
4. *Logistics*—This section focuses on the logistical support that every event requires, including equipment, personnel, supplies, and infrastructure support.
5. *Finance*—This section accounts for and manages all money that is spent during responding to a disaster. While immediate costs and purchases during a disaster tend to be supported by affected communities and hospitals, accurate purchasing records, inventory records, personnel costs, and transportation costs must be carefully managed in order to recoup costs after the event.

The Hospital Incident Command System (HICS) manages the response within the hospital and coordinates the hospital's efforts with the overall community response. The HICS is led by an incident commander within the hospital. The hospital's incident commander and the community incident commander

communicate with each other directly through telephone, radio, computer, or via liaison personnel. The organization and leadership of the HICS is usually different than organizational structure and leadership of day-to-day hospital operations [4]. What works for managing the daily business of a hospital oftentimes does not work well for managing the response to a crisis. Therefore, hospitals, and their intensive care units (ICUs), must assign personnel to specific HICS positions as part of their disaster preparedness planning. Each individual assigned to an HICS position has specific duties that must be performed prior to, during, and following the disaster response. It is imperative that all HICS personnel be fully trained for the duties they are required to perform.

Modular Emergency Medical Systems

The Modular Emergency Medical System, or MEMS, is a community emergency medical care system consisting of temporary facilities that can be quickly set up to supplement hospital care during a disaster. This system provides a conceptual framework for managing a surge in patients who require screening, triage, antibiotic treatment, immunizations, prophylaxis, or noncritical inpatient care. The MEMS helps hospitals to maximize their critical care capacity during a disaster by providing temporary, alternate facilities that can care for noncritical patients in their respective communities.

The major MEMS components are Neighborhood Emergency Help Centers (NEHC) and Acute Care Centers (ACC). Both types of centers can provide screening and triage. The NEHC provides routine, nonurgent outpatient care. The ACC can provide inpatient care to acutely ill noncritical patients. The ACC can receive patients directly from the incident, or be a facility to which hospitals can offload stable inpatients in order to free up hospital critical care bed space during overwhelming events. Local or regional authorities can open an NEHC or an ACC under two scenarios: (i) when a federal public health incident or a federal disaster is declared or (ii) when the state governor has issued a state of emergency. Both types of temporary facilities will operate under the command and control of the local community ICS with support from a Regional Multiagency Command [5].

How Does Critical Care Fit into the MEMS Plan?

The hospital is only place where critical care can be provided immediately after a disaster. Therefore, the community's medical surge plan must address how to protect the hospital from being overwhelmed with patients during a disaster. A carefully executed MEMS plan allows hospitals to offload stable patients to an ACC. This will help to prevent the hospital from being overwhelmed during a disaster and allow the hospital to expand its critical care capabilities by utilizing non-ICU hospital beds for critical care, if necessary.

Refining Surge Capacity

Hick and colleagues suggest a classification for surge capacity that may aid hospitals and communities in their planning for a major disaster [6]. They categorize surge capacity into three levels:

- *Conventional capacity*—This level would be implemented in major mass-casualty incidents that trigger activation of the hospital emergency operations plan. The resources used (spaces, staff, and supplies) would be consistent with the hospital's usual care levels.
- *Contingency capacity*—This level would be used temporarily during a major mass casualty incident, or on a longer-term basis during a disaster whose medical demands exceeded community resources. The resources would require adaptations to medical care spaces, staffing constraints, and supply shortages, but without significant impact on the medical care that is delivered.
- *Crisis capacity*—This level would be implemented in catastrophic situations that result in a significant impact on standard of medical care that can be provided. Severe limitations of space, staff, and supplies would not allow hospitals to provide the usual standard of medical care. If surge capacity reaches the crisis level, resources would be allocated in a way that facilitates the best possible medical care with the limited resources that are available.

It is recommended that hospitals and their critical care units develop disaster preparedness plans that contain specific criteria for each level of surge capacity. It is important to note that the same disaster event might have very different effects on different hospitals, depending on the institution's size. For example, an eight-victim automobile crash may require a conventional level of surge capacity for a large hospital that has a level 1 trauma center, but could require a contingency or crisis level of surge capacity for a small community hospital.

CRITICAL CARE IN DISASTERS

Current Status

From 2002 to 2007, the Hospital Preparedness Program of the U.S. Department of Health and Human Services spent $2.2 billion to support medical preparedness goals, which included improvement of hospital surge capabilities [7]. However, in 2008 the U.S. General Accounting Office reported that many states are still not adequately prepared to respond effectively to a catastrophic event, such as pandemic influenza, in which medical resources could become overwhelmed and there would be a need to change the way medical care is provided by altering or adjusting the care pathways [8]. During a major disaster, nothing will challenge hospitals more than attempting to provide high-quality critical care with limited resources.

Traditionally, most hospitals have focused their disaster planning on trauma care capabilities. However, the advent of severe acute respiratory syndrome (SARS) and the risk of an H1N1 influenza pandemic have caused hospitals to consider their overall critical care capability, to include medical critical care, as an important component of disaster response plans. For example, it is estimated that without adequate critical care resources during the 2003 SARS outbreak in Toronto, the case fatality rate would have been approximately 20%, compared to the 6.5% case fatality rate that actually occurred [9]. These data highlight the importance of including the overall critical care capabilities of hospitals in disaster planning efforts, not just the capabilities for trauma care.

At present, it is estimated that the average daily occupancy rate of critical care beds in the United States is 65%. This suggests that some hospitals may have the capability to expand critical care services during a disaster, assuming that staff and supplies are available [10]. However, even with normal excess capacity, there does not appear to be a sufficient number of critical care beds to meet the demands of a pandemic that might affect the entire nation at the same time. It is estimated that critically ill patients who are not cared for in an ICU have a threefold mortality rate compared with those who are cared for in an ICU [11]. Thus, if critical care capabilities become overwhelmed by large numbers of critically ill or injured patients during a disaster, high mortality rates are likely to occur.

Surging Assets to Optimize Critical Care Capability

In planning for surge capacity during disasters, hospitals need to prepare for events that have a sudden impact and are of relatively short duration, such as transportation accidents,

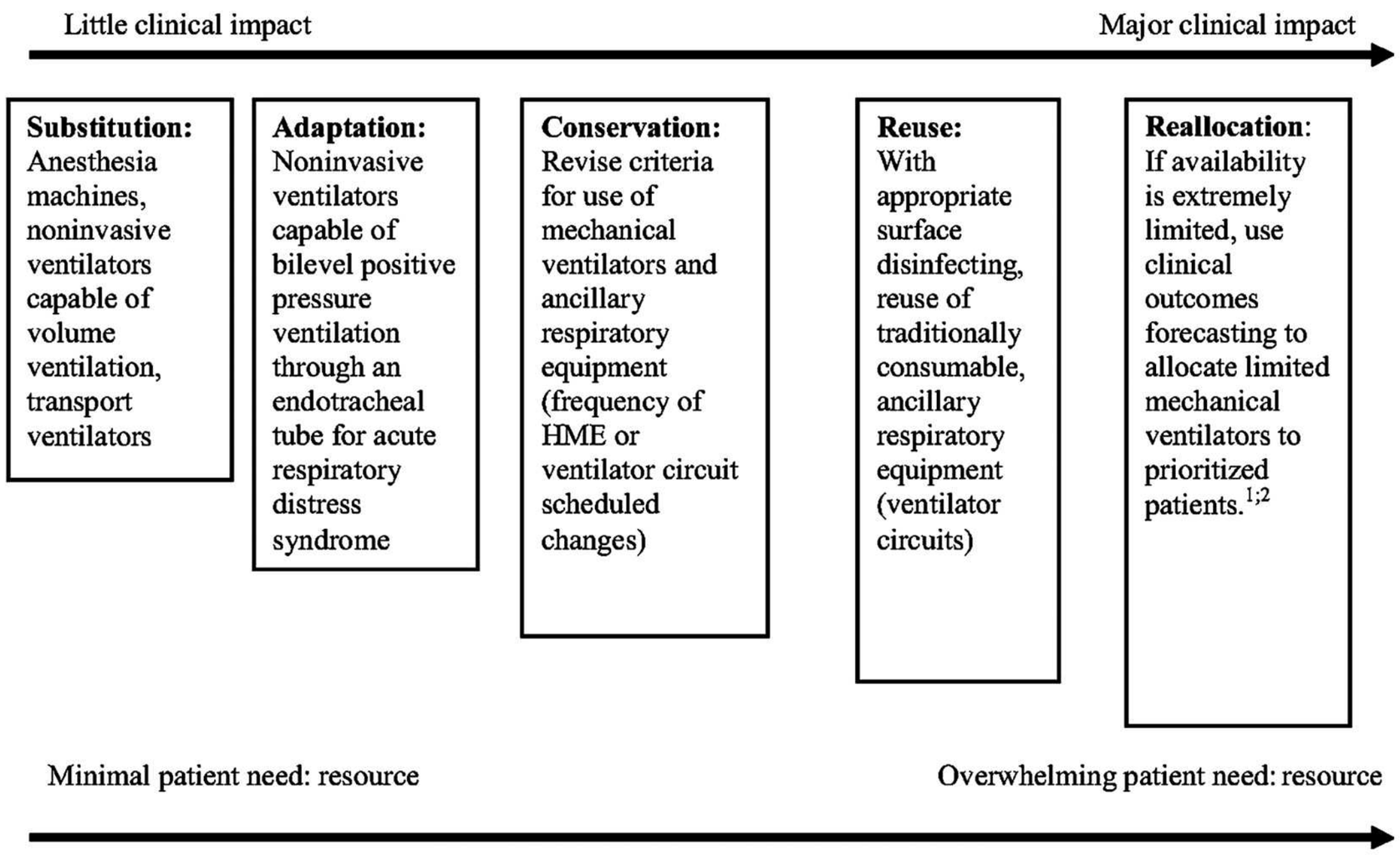

FIGURE 216.1. Stepwise modifications in resource use to maintain positive-pressure ventilation. HME, heat and moisture exchanger. [From Rubinson L, Hick JL, Hanfling DG, et al: Definitive care for the critically ill during a disaster: a framework for optimizing critical care surge capacity. *Chest* 133:18S–31S, 2008.]

explosions, bombings, as well as more prolonged events, such as earthquakes, hurricanes, and influenza pandemics [12,13].

A common rubric for the planning of critical care surge capacity places critical care resources into three categories: "*stuff*"—the medical supplies and equipment necessary for providing critical care; "*staff*"—the availability of trained critical care providers and support personnel; and "*space*"—the physical space within the hospital that can be used to provide critical care to a large number of critically ill or injured patients [14]. In all disaster situations, the effective utilization of critical care surge capacity will ultimately depend on the training and effectiveness of the hospital and community incident command systems which must execute surge capacity plans [15].

Stuff

Patients requiring care beyond the levels available on medical-surgical wards are generally admitted to ICUs because of monitoring needs, the need for intensive-care nursing, or the need for treatment with special equipment. The provision of mechanical ventilation is the most common requirement needed to manage critically ill patients with respiratory compromise. The main challenge in providing this important therapeutic modality during a disaster is the availability of mechanical ventilators.

The United States has approximately 62,000 full-feature ventilators or 20 of these per 100,000 residents (52 pediatric full-feature ventilators per 100,000 children under age 14). Approximately 100,000 ventilators that are less than full-feature are also available [16]. In any disaster with a large number of critically ill patients, it is likely that the availability of mechanical ventilators will rapidly decrease. Thus, in preparing to provide mechanical ventilation to a large number of critically ill disaster casualties, planners need to consider other options, such as anesthesia machines or noninvasive positive-pressure ventilation. Although these alternatives are not ideal for infection control, and their use may be limited by a lack of skilled respiratory therapists, they may be the best available options in a major disaster [17,18,19]. A systematic stepwise approach for providing positive-pressure ventilator support as resources become progressively scarce during a disaster is illustrated in Figure 216.1.

In considering the use of mechanical ventilators during a disaster, it is recommended that emergency response personnel should not rely on ventilators that operate on high-pressure medical gas. This is because such devices typically require a large amount of oxygen, which is likely to be in short supply during a prolonged event, especially if there are large numbers of casualties with respiratory problems. The most common form of hospital oxygen is liquid oxygen. The technical difficulties involved in supplying, storing, generating, and concentrating this kind of oxygen make it virtually impossible to increase supplies to a level that will meet the high demand caused by a large number of critically ill patients [20]. Finally, both mechanical ventilator and oxygen vendors may have multiple contracts with different hospitals within a region; such contract duplication could result in major shortages if all hospitals in a region require increased support simultaneously.

In order to support the need for additional mechanical ventilators during a disaster, both the United States and Canada have prepositioned stockpiles of sophisticated transport ventilators throughout their respective countries. The United States has at least 4,600 prepositioned ventilators at the present time [21]. Three types of transport ventilators are currently available in the United States stockpiles: Impact 754, Pulmonetic Systems LTV-1200, and Puritan Bennett LP-10 [22]. Access to these ventilators during a disaster would be provided by the federal government through a formal request from an affected state [23]. In addition, many states and regions are developing their own mechanical ventilator stockpiles along with plans for distributing the stockpiled ventilators to affected areas during a disaster.

The provision of critical care during a disaster will also require that a large quantity of supplies and pharmaceuticals be on hand and readily available to critical care providers. In 2005, during the Hurricane Katrina disaster in New Orleans, the lack of available supplies, pharmaceuticals, and operational equipment forced the dedicated providers at Charity Hospital

to improvise critical care practices and deviate from the usual standards of care prior to final evacuation of the hospital [24]. This unfortunate incident illustrates the importance of carefully planning for the increase in supplies, pharmaceuticals, and infrastructure that will be needed to provide critical care during a prolonged disaster. The Task Force for Mass Critical Care convened in 2007 by the American College of Chest Physicians (hereafter referred to as "the Task Force") recommends that hospitals should be prepared to triple their normal daily critical care capacity for 10 days without external assistance [25].

Staff

A significant challenge in maintaining critical care capability during a disaster will be the availability of a sufficient number of trained personnel. Shortages of intensivists, critical care nurses, respiratory therapists, critical care pharmacists, or other specially trained personnel may be a limiting factor in caring for large numbers of critically ill patients. Such limitations could be especially problematic in settings such as pandemic influenza, where providers might be ill, or might choose not to work because of personal safety fears or the need to care for ill family members [26]. Lastly, many critical care providers also play important emergency response roles in their communities; this is especially prevalent in nonurban settings. Such "dual-hat" responsibilities could impact the availability of critical care providers in hospitals during a major disaster.

In reviewing critical care staffing requirements during a disaster, the Task Force endorsed previously published recommendations on the surging of staff [14]. In short, the most experienced providers should perform direct patient care, if feasible. Those providers not normally operating in critical care settings should be cross-trained, or retrained, on essential bedside skills in the ICU as part of a hospital's disaster preparedness program. Finally, systematic procedures (such as protocols) should be instituted and understood by all critical care providers, in order to standardize processes, maximize good outcomes, and maximize safety to patients and staff during a disaster.

While intensivists are the most highly trained critical care physicians and should provide direct patient care to the extent feasible, in surge conditions they will need to focus part of their effort on supervising cross-trained physicians from other specialties. In such a situation, intensivists should only provide direct care for patients who require complex treatment or procedures. Nonintensivist physicians who are skilled in proving hands-on care, such as hospitalists, inpatient pediatricians, general surgeons, or anesthesiologists, could be assigned six patients each. Intensivists could supervise 4 to 8 such providers, thereby extending their critical care expertise to almost 50 patients. Similarly, critical care nurses understand the need for matching nursing staff with patient acuity. ICU charge nurses could, therefore, match several non-ICU nurses to appropriate patients within a "pod" of patients that are overseen by an ICU nurse, leaving only the most complex patients under the sole care of other ICU nurses. Another approach could be to assign specific bedside care procedures to non-ICU nurses (bathing, vital signs, catheter management, medication delivery, etc.), thereby permitting ICU nurses to oversee the provision of specific critical nursing care to several patients. Respiratory therapists usually provide care to four to six ICU patients, in accordance with the American Association for Respiratory Care Uniform Reporting Manual. Surge requirements may mandate a higher ratio of patients per therapist, ICU therapists supervising outpatient or non-ICU therapists, or even ICU therapists directing non-therapists in basic respiratory care. Finally, oncology, outpatient, radiation, or other non-ICU pharmacists may similarly be asked to support critical care operations under the tutelage of critical care pharmacists. Variants of these options already occur, for example, during off hours, or during brief surges such as mass casualty setting. Training for, rehearsing and streamlining such processes will become necessary for prolonged events that will severely strain staff resources during a major disaster [20].

Space

ICUs are highly sophisticated areas where complex equipment requirements are married with highly skilled and specialized staff in order to maximize patient outcomes. However, during a major disaster space limitations may require that critical care be provided in other areas of a hospital [27,28]. If it becomes necessary to provide critical care outside of an ICU during a major disaster, it should be provided in those areas of a hospital that are most analogous to an ICU.

In the initial phases of a surge requirement, hospitals should be able to accommodate small increases in critically ill patients with minimal impact, assuming that "stuff" and "staff" are available and the hospital is not at maximum capacity. Stable ICU patients requiring minimal care or monitoring can be transferred to step-down units, telemetry areas, postanesthesia care units, surgical centers, or other ambulatory care settings, as appropriate. In this event, the hospital bed space should be decompressed by transferring stable ward patients to home care, to skilled nursing facilities, or to alternate community facilities such as an ACC. As an emergency mass critical care event progresses, formal critical care space will need to expand into other areas of the hospital, with the hospital continuing to make room for critically ill patients by transferring the most stable inpatients elsewhere.

An alternative to expanding internal ICU capability is for communities to develop and deploy "field" ICUs. Critical care has been provided in such settings before, and can be especially relevant and appropriate when hospitals have been physically destroyed or incapacitated [29–31]. However, because of the logistical requirements for specialized equipment, infection control support, and the relocation of trained personnel, critical care should only be provided in "field" settings as a last resort. In most major disaster situations, such facilities can be best used for the management of noncritically ill patients who are transferred from hospitals in order to free up space for the management of the critically ill. The Task Force recommends using alternate sites, or buildings of convenience, for critical care only if a region's medical facilities are physically destroyed or rendered unsafe to occupy [20].

RESOURCE ALLOCATION AND TRIAGE DURING TIMES OF OVERWHELMING DEMAND

The Greatest Good for the Greatest Number of Victims

The goal of surging critical care resources during a disaster is to provide the greatest good for the greatest number of event victims. Critical care providers and institutions should strive to manage resources within their own facility and region with the goal of providing usual critical care practices to the extent possible. However, in a major disaster, as resources become increasingly limited, healthcare providers and leaders must have a plan in place to change the focus of critical care from the needs of the individual to the needs of the population as a whole. This requires a defined triage plan to be developed, communicated, and implemented fairly.

Ethical and Legal Principles

Utilitarian principles guide the theory of the "greatest good for the greatest number." In times of overwhelming resource constraints, limited capabilities should be targeted to those with the greatest likelihood of benefitting from the care. Those who are unlikely to recover or improve with the available care are not abandoned, but are provided with appropriate palliative care. This fundamental principle guides the implementation of a mass-casualty triage system during major disasters [32].

The Task Force supports the concept that if surge measures do not meet demand, then individual autonomy will be limited. It mandates a fair and just rationing of resources, based on objective information and decision-making, in order to benefit the population as a whole, rather than individual patients. Such a shift in healthcare priorities requires active community involvement and an open, transparent decision-making processes. Ideally, plans for the fair and just rationing of critical care resources during periods of overwhelming demand should be developed prior to the disaster. "Procedural justice" requires absolute conformity to the agreed-upon process, which itself must be repeatedly reevaluated and validated through ongoing, real-time epidemiological investigation [33].

Importantly, in order to implement such processes, providers must feel secure in their legal protection. Hence, providers must be legally protected from local and state law if there is a need to deviate from the usual standards of care during periods of scarce resources. The need for such legal protection was poignantly highlighted in New Orleans during the Hurricane Katrina disaster, as palliative care was provided to some patients as evacuation attempts were repeatedly delayed and hospital capabilities were overwhelmed [34]. Several states have begun efforts to address this important issue [35,36]. The Task Force recommends that uniformly accepted, predetermined algorithms be developed for triaging critically ill patients during a disaster, with adherence to these algorithms being sufficient to provide necessary legal protection to providers and other decision makers [33].

Critical Care Triage

Triage processes have been well described for the prehospital and emergency department mass-casualty events, such as the use of START (Simple Triage and Rapid Treatment) cards [37]. However, ICU triage processes and procedures have not been well studied or validated in overwhelming critical care disasters. The Task Force recommends that planning for the triage of critically ill patients during a major disaster should include well-defined "triggers" that promptly alert hospital and community leadership to the fact that critical care resources are being overwhelmed and there is a need to direct the use of a triage process. Such triggers would include a lack of critical equipment or medical supplies, inadequate critical care spaces, inadequate staff, and inadequate capability to transfer noncritically ill patients to other facilities.

Once the requirement to triage care has been directed, critical care providers must determine which patients should receive critical care and which patients should not. This process needs to be carefully planned and evaluated with community

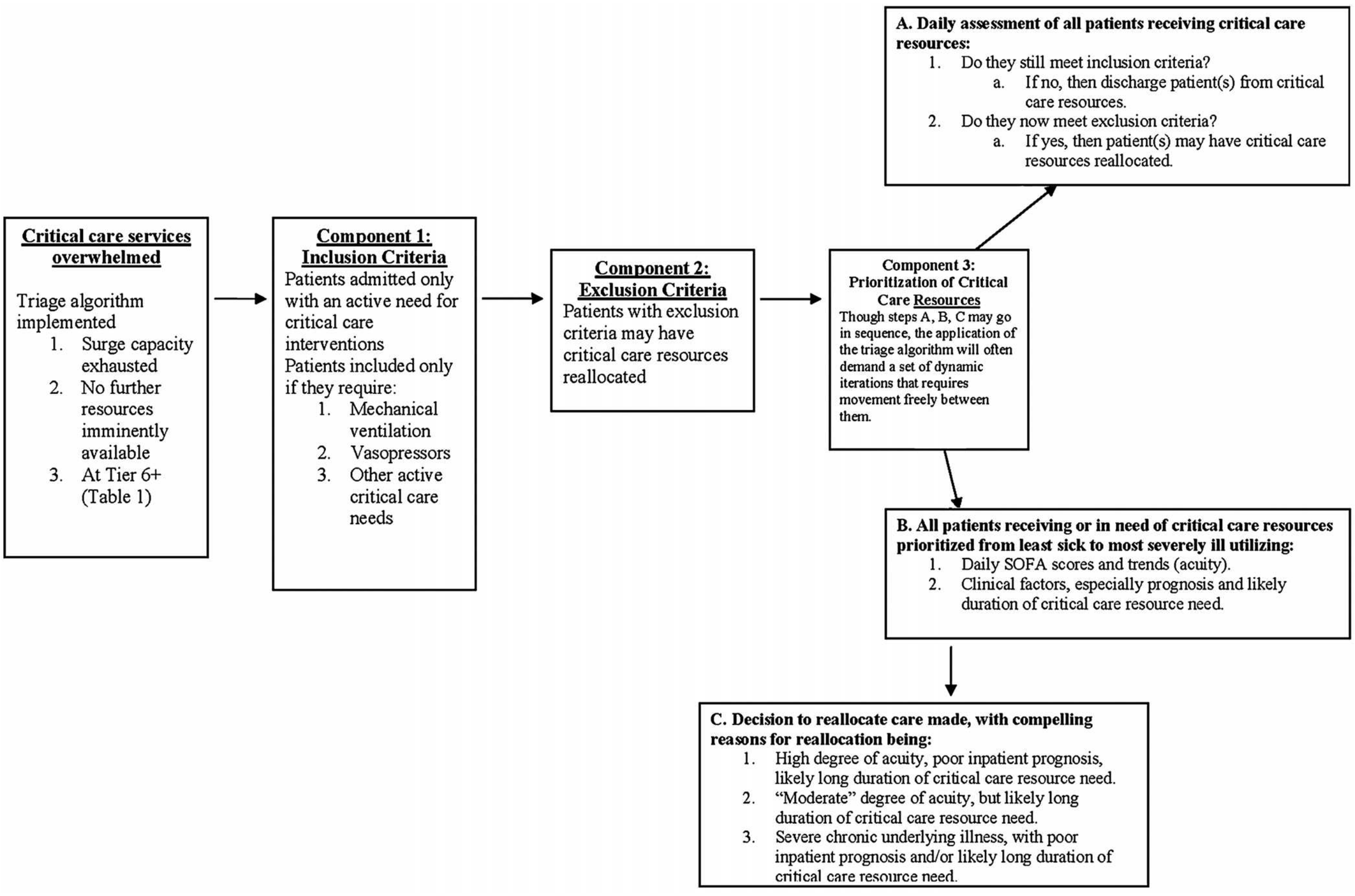

FIGURE 216.2. Critical care triage algorithm. [From Devereaux AV, Dichter JR, Christian MD, et al: Definitive care for the critically ill during a disaster: a framework for allocation of scarce resources in mass critical care. *Chest* 133:51S–66S, 2008.]

involvement prior to a catastrophic event. If, for example, a healthcare system or region proposes to exclude critical care to the very elderly during a major disaster, then community representatives from the elderly population would need to be included in such decisions. That is, the elderly would participate in advance planning with providers on how to triage the elderly in future mass-casualty emergencies.

Several severity-of-illness models have been developed for the ICU setting that may be applied to the triage process. However, all have similar limitations in that they have not been rigorously evaluated in emergency mass critical-care scenarios. The Task Force and other groups have advocated the use of the Sequential Organ Failure Assessment (SOFA) score because of its demonstrated effectiveness in the ongoing assessment of critically ill patients and the ease with which it can be calculated with minimal laboratory requirements [33,38].

The Task Force recommends that hospitals establish a critical care triage team for the effective and ethical triage of critically ill patients. It recommends that the triage team consist of a small group of experienced providers to include an intensivist, a critical care nurse, a respiratory therapist or pharmacist, and a hospital administrator. This group, operating independently from the bedside clinicians, would gather periodic SOFA scores to determine the severity of illness and document improvement, stability, or deterioration of critically ill patients over time. The Task Force recommends that patients with high SOFA scores (> 11) not be offered critical care. Similarly, patients who deteriorate or fail to improve over time would have their critical care resources reallocated to other patients (Fig. 216.2). The availability of an experienced critical care triage team has the advantage of removing the burden of triage decisions from busy clinicians who are providing critical care at the bedside. In the HICS, the critical care triage team should operate under the command of the Hospital Operations Section Chief.

In order to assure compliance and integrity of the triage process, the Task Force recommends that a review committee be established to oversee triage plans and operations. This committee, distinct from the triage team, would:

- Work with regional planners and maintain situational awareness in the community and state, regarding the ongoing use and need of triage protocols;
- Review the implementation of the local triage protocol, to ensure compliance and integrity of triage operations;
- Serve as a forum for appeals by patients, families, and staff regarding the accurate and ethical implementation of the triage tool; and
- Participate in the real-time epidemiological evaluation of the catastrophic event, to help public health and other officials determine the ongoing validity of the SOFA score as a triage tool for critically ill patients.

SUMMARY

Preparing ICUs for disasters requires a methodical approach within a defined organizational structure in order to optimize care for large numbers of critically ill patients. Ideally, hospitals are the optimal setting to provide critical care for severely ill and injured patients. During major disasters, hospitals should coordinate with community medical response systems to offload patients with minor injuries or illnesses so that hospital resources can be focused on the care of critically ill patients.

Predisaster planning and training are essential for mitigating the adverse effects of an overwhelming disaster on hospitals and their communities. Carefully developed plans for surging critical care "stuff, staff, and space" will facilitate continuation of usual critical care processes for as long as possible. However, if surge procedures fail to meet the critical care demands of an overwhelming patient influx, processes to triage and alter the usual standards of critical care must be implemented. The planning concepts and guidelines outlined in this chapter can help guide critical care practitioners to care for their patients under the challenging conditions of a catastrophic disaster.

DECLARATION

The opinions and assertions contained herein are those of the authors and do not necessarily reflect the views or position of the Department of Veterans Affairs, or the academic institutions with which the authors are affiliated.

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APPENDIX

JOSEPH J. FRASSICA

CALCULATIONS COMMONLY USED IN CRITICAL CARE

JOSEPH J. FRASSICA

TABLE OF CONTENTS

ABBREVIATIONS USED IN THE APPENDIX

A	Alveolar	atm	Atmosphere
D	Dead	BSA	Body surface area
E	Expiration	cap	Capillary
I	Inspiration	cr	Creatinine
P	Pressure	dyn	Dynamic
$\dot{Q}$	Net liquid flow	is	Interstitium
R	Respiratory quotient	st	Static
T	Tidal	ICP	Intracranial pressure
V	Volume	a	Arterial
Δ	Change	d	Distribution
H	Viscosity	l	Length
Π	Oncotic pressure	r	Radius
Σ	Permeability	t	Time
		$\bar{v}$	Mixed venous

FAHRENHEIT AND CELSIUS TEMPERATURE CONVERSIONS

°C	°F	°C	°F
45	113.0	32	89.6
44	111.2	31	87.8
43	109.4	30	86.0
42	107.6	29	84.2
41	105.8	28	82.4
40	104.0	27	80.6
39	102.2	26	78.8
38	100.4	25	77.0
37	98.6	24	75.2
36	96.8	23	73.4
35	95.0	22	71.6
34	93.2	21	69.8
33	91.4	20	68.0

DOSAGE AND ACTION OF COMMON INTRAVENOUS VASOACTIVE DRUGS

	Dosage	α	β_1	β_2
Dopamine	1–2 µg/kg/min	+	+	0
	2–10 µg/kg/min	++	+++	0
	10–30 µg/kg/min	+++	++	0
Dobutamine	2–30 µg/kg/min	+	+++	++
Norepinephrine	0.05–1 mg/kg/min titrate to effect	+++	++	+
Epinephrine	0.1–1.0 mg/kg/min	++	+++	+++
Isoproterenol	2–10 µg/min	0	+++	+++
Phenylephrine	0.1–0.5 mg/kg/min	+++	0	0
Milrinone	(Loading dose 50 mg/kg over 10–15 min)			
	0.375–0.75 mg/kg/min	—	—	—
Labetolol	2 mg/min; max dose 300 mg	—	—	—
Esmolol	50–300 mg/kg/min	—	—	—

HEMODYNAMIC CALCULATIONS

MEAN BLOOD PRESSURE (mm Hg)

$$= \overline{BP}$$

$$= \frac{\text{Systolic BP} + (2 \times \text{Diastolic BP})}{3}$$

$$= \text{Diastolic BP} + \frac{1}{3}(\text{Systolic BP} - \text{Diastolic BP})$$

Normal values: 85–95 mm Hg

THE FICK EQUATION FOR CARDIAC INDEX (L/min/m^2)

$$= \text{CI}$$

$$= \frac{\text{CO}}{\text{BSA}}$$

$$= \frac{\text{Oxygen consumption}}{\text{Arterial } O_2 \text{ contemt} - \text{Venous } O_2 \text{ content}}$$

$$= \frac{10 \times \dot{V}O_2\,(\text{mL/min/m}^2)}{\text{Hgb (g/dl)} \times 1.39}$$

$$\times (\text{Arterial \% saturation} - \text{Venous \% saturation})$$

Normal values: 2.5–4.2 L/min/m^2

STROKE INDEX (mL/beat/m^2)

$$= \frac{\text{CI (L/min/m}^2) \times 1{,}000}{\text{Heart rate (beats/min)}}$$

Normal values: 33–47 mL/beat/m^2

SYSTEMIC VASCULAR RESISTANCE (dyne/sec/cm^5)

$$= \text{SVR}$$

$$= \frac{80 \times (\text{Arterial } \overline{\text{BP}} - \text{Right atrial } \overline{\text{BP}})}{\text{CO (L/min)}}$$

Normal values: 770–1,500 dyne/sec/cm^5

PULMONARY VASCULAR RESISTANCE (dyne/sec/cm^5)

$$= \text{PVR}$$

$$= \frac{80 \times (\text{Pulmonary artery } \overline{\text{BP}} - \text{Pulmonary capillary wedge pressure})}{\text{CO (L/min)}}$$

Normal values: 20–120 dyne/sec/cm^5

TOTAL PULMONARY RESISTANCE (dyne/sec/cm^5)

$$= \text{TPR}$$

$$= \frac{80 \times \text{Pulmonary artery } \overline{\text{BP}}}{\text{CO (L/min)}}$$

CAPILLARY FLUID FILTRATION

$$= \dot{Q}_f$$

$$= k(P_{cap} - P_{is}) - k\sigma(\pi_{cap} - \pi_{is})$$

NUTRITIONAL CALCULATIONS

BODY MASS INDEX

$$= \text{BMI}$$

$$= \frac{\text{Weight (kg)}}{(\text{Height [cm]})^2}$$

CALORIC CONTENT OF FOODS

Food type	kcal/g	Range
Carbohydrate	3.4	3.4–4.1
Protein	4.0	3.3–4.7
Fat	9.1	9.1–9.5

RESPIRATORY QUOTIENT

$$= \frac{CO_2 \text{ production (mL/min)}}{O_2 \text{ consumption (mL/min)}}$$

$$= \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

RELATIONSHIP OF FUEL BURNED TO RESPIRATORY QUOTIENT

Fuel	*R*
Ketones	< 0.6
Fat	0.7
Carbohydrate	1.0
Lipogenesis	> 1.0

NITROGEN BALANCE

$$= \text{Nitrogen consumed} - \text{Nitrogen excreted}$$

$$= \frac{\text{Protein calories (kcal/day)}}{25} - \text{Urine nitrogen (g/day)} - 5\ (\text{g/day})$$

HARRIS–BENEDICT EQUATION OF RESTING ENERGY EXPENDITURE (kcal/day)

$$\text{Males} = 66 + (13.7 \times \text{Weight [kg]}) + (5 \times \text{Height [cm]}) - (6.8 \times \text{Age})$$

$$\text{Females} = 655 + (9.6 \times \text{Weight [kg]}) + (1.8 \times \text{Height [cm]}) - (4.7 \times \text{Age})$$

WEIR EQUATION (MODIFIED) OF ENERGY EXPENDITURE (kcal/day)

$$= (3.94 \times \dot{V}_{O_2}\,[\text{mL/min}]) + (1.11 \times \dot{V}_{CO_2}\,[\text{mL/min}])$$

TYPICAL DRUG DOSAGES FOR RAPID SEQUENCE INTUBATION

Muscle relaxants	
Rocuronium	0.6–1.2 mg/kg
Succinylcholine	1 mg/kg
Vecuronium	0.1–0.20 mg/kg
Sedatives	
Etomidate	0.3–0.4 mg/kg
Ketamine	1–2 mg/kg
Propofol	1–2 mg/kg
Thiopental	3–4 mg/kg

PULMONARY CALCULATIONS

TIDAL VOLUME

$= V_T$
$=$ Dead space + Alveolar space
$= V_D + V_A$

ALVEOLAR GAS EQUATION

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R}$$
$$= FIO_2(P_{atm} - P_{H_2O}) - \frac{PaCO_2}{R}$$
$$= 150 - \frac{PaCO_2}{R} \text{(room air, sea level)}$$

ALVEOLAR ARTERIOLAR GRADIENT

$= A - a$ gradient
$= PAO_2 - PaO_2$

Normal values (upright): 2.5 + (0.21 × age)

ALVEOLAR VENTILATION (L/min)

$= \dot{V}_E$
$$= k\frac{\dot{V}CO_2}{PaCO_2}$$
$$= \frac{0.863 \times \dot{V}_{CO_2}(\text{mL/min})}{Pa_{CO_2}(1 - V_D/V_T)}$$

Normal values: 4–6 L/min

BOHR EQUATION OF DEAD SPACE

$$V_D/V_T = \frac{PACO_2 - PECO_2}{PACO_2}$$

Normal values: 0.2–0.3

PHYSIOLOGIC DEAD SPACE

$$V_D/V_T = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

Normal values: 0.2–0.3

OXYGEN DISSOLVED IN BLOOD (mL/dL)

$= Do_2$
$= 0.003\,(\text{mL}\,O_2/\text{dL}) \times PaO_2\,(\text{mm Hg})$

OXYGEN CAPACITY OF HEMOGLOBIN (mL O_2/dL)

$= 1.39\,(\text{mL}\,O_2) \times \text{Hgb}\,(\text{g/dL})$

Normal values: 17–24 mL/dL

OXYGEN CONTENT OF THE BLOOD (mL/dL)

$= Co_2$
$= D_{O_2} + (1.39 \times \text{Hgb}\,[\text{g/dL}] \times [\%\ \text{Hgb saturated with}\ O_2])$
$= D_{O_2} + (1.39 \times \text{Hgb}\,[\text{g/dL}] \times S_{O_2})$

Normal values: 17.5–23.5 mL/dL

PERCENTAGE OF SATURATION OF HEMOGLOBIN WITH OXYGEN

$= SO_2$
$$= 100 \times \frac{CO_2 - DO_2}{1.39 \times \text{Hgb}\,(\text{g/dL})}$$

Normal values: > 95%

PHYSIOLOGIC SHUNT

$= \dot{Q}_S/\dot{Q}_T$
$$= \frac{C_{capo_2} - C_{O_2}}{C_{capo_2} - C_{\bar{v}O_2}}$$
$$= \frac{1.39 \times \text{Hgb}\,(\text{g/dL}) + 0.003 \times PaO_2 - CaO_2}{1.39 \times \text{Hgb}\,(\text{g/dL}) + 0.003 \times PaO_2 - C\bar{v}O_2}$$

Normal values: < 5%

COMPLIANCE

$= \Delta V/\Delta P\,(\text{mL/cm}\,H_2O)$

On Mechanical Ventilation

$$\text{Static compliance} = C_{st} = \frac{V_T}{P_{plateau} - P_{end\,exp}}$$

$$\text{Dynamic effective complicance} = C_{dyn} = \frac{V_T}{P_{peak} - P_{end\ exp}}$$

During Spontaneous Breathing

$$\text{Compliance of the lung} = C_L = \frac{V_T}{P_{alveolus} - P_{pleura}}$$

$$\text{Compliance of the chest wall} = CW_{cw} = \frac{V_T}{P_{pleura} - P_{atm}}$$

$$\text{Compliance of the respiratory system} = C_{rs} = \frac{V_T}{P_{alveolus} - P_{atm}}$$

Normal values: C_{st} > 60 mL/cm H_2O; C_{dyn} > 60 mL/cm H_2O
C_L > 200 mL/cm H_2O; C_{rs} > 100 mL/cm H_2O

RESISTANCE—OHM'S LAW

$$= \Delta P/\text{flow} = \Delta P/\dot{Q}$$

Normal values: airway resistance of the lung at functional residual capacity (FRC) = 2 cm H_2O/L/sec

WORK-OF-BREATHING

$$W_{\text{Thorax}} = \int_{t_1}^{t_2} (P_{\text{aw}} - P_{\text{atm}})\dot{V}\,dt$$

$$W_{\text{Lung}} = \int_{t_1}^{t_2} (P_{\text{aw}} - P_{\text{es}})\dot{V}\,dt$$

$$W_{\text{Chest wall}} = \int_{t_1}^{t_2} (P_{\text{es}} - P_{\text{atm}})\dot{V}\,dt$$

Normal values: W_{thorax} = 0.5 kg-M/min

LAPLACE'S LAW OF SURFACE TENSION OF A SPHERE

$$P = 2T/r$$

POISEUILLE'S LAW OF LAMINAR FLOW

$$\dot{V} = \frac{P\pi r^4}{8\eta l}$$

COMPOSITION AND PROPERTIES OF COMMON INTRAVENOUS SOLUTIONS

Solution	Na^+	Cl^-	K^+	Ca^+	Lactate	Kcal/L	mOsm/L
D5W	0	0	0	0	0	170	252
D10W	0	0	0	0	0	240	505
D50W	0	0	0	0	0	1,700	2,530
1/2 NS	77	77	0	0	0	0	154
NS	154	154	0	0	0	0	308
3% NaCl	513	513	0	0	0	0	1,026
Ringer's lactate	130	109	4	3	28	0	308
20% mannitol	0	0	0	0	0	0	1,098

ELECTROLYTE AND RENAL CALCULATIONS

ANION GAP

$$= [Na^+] - [Cl^-] - [HCO_3^-]$$

Normal values: 9–13 mEq/L

EXPECTED ANION GAP IN HYPOALBUMINEMIA

$$= 3 \times (\text{albumin [g/dL]})$$

CALCULATED SERUM OSMOLALITY

$$= 2[Na^+] + \frac{[\text{Glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

Normal values: 275–290 mOsm/kg

OSMOLAR GAP

= Serum osmolality measured − Serum osmolality calculated

Normal values: 0–5 mOsm/kg

Na^+ AND GLUCOSE

$[Na^+]$ decreases 1.6 mEq/L for each 100 mg/dL increase in [glucose]

TOTAL CALCIUM AND ALBUMIN

Corrected calcium (mg/dL) = Measured total calcium (mg/dL) + 0.8(4.0 − serum albumin)

GLOMERULAR FILTRATION RATE = GFR

$$\text{Measured} = \text{Creatinine clearance} = \frac{U_{\text{Creat}}V}{P_{\text{Creat}}}$$

$$= \frac{[\text{Creatinine}]_{\text{urine}}\ (\text{g/dL}) \times \dfrac{\text{Urine volume (mL/day)}}{1{,}440\ (\text{minute/day})}}{[\text{Creatinine}]_{\text{plasma}}\ (\text{mg/dL})}$$

$$\text{Estimated for males} = \frac{(140 - \text{Age}) \times (\text{Lean body weight [kg]})}{P_{\text{Creat}} \times 72}$$

Estimated for females = 0.85 × Male estimate

Normal values: 74–160 mL/min

WATER DEFICIT IN HYPERNATREMIA (L)

$$= 0.6 \times (\text{Body weight [kg]}) \times \left(\frac{[Na^+]}{140} - 1\right)$$

WATER EXCESS IN HYPONATREMIA (L)

$$= 0.6 \times (\text{Body weight [kg]}) \times \left(1 - \frac{[Na^+]}{140}\right)$$

FRACTIONAL EXCRETION OF SODIUM

$$= F_E\,Na$$

$$= \frac{\text{Excreted } Na^+}{\text{Filtered } Na^+} \times 100$$

$$= \frac{U_{Na^+} \times V}{\text{GFR}} \times [Na^+] \times 100$$

$$= \frac{U_{Na^+}/[Na^+]}{U_{\text{Creat}}/[\text{Creat}]}$$

ACID–BASE FORMULAS

HENDERSON–HASSELBALCH EQUATION

$$\text{pH} = pK + \log\frac{[HCO_3^-]}{0.03 \times PaCO_2}$$

HENDERSON'S EQUATION FOR CONCENTRATION OF H^+

$$[H^+](\text{nM/L}) = 24 \times \frac{PaCO_2}{[HCO_3^-]}$$

METABOLIC ACIDOSIS

Bicarbonate deficit (mEq/L) = 0.5 × (Body weight [kg]) × (24 − $[HCO_3^-]$)

Expected PCO_2 = 1.5 × $[HCO_3^-]$ + 8 ± 2

METABOLIC ALKALOSIS

Bicarbonate excess = 0.4 × (Body weight [kg]) × ($[HCO_3^-]$ − 24)

RESPIRATORY ACIDOSIS

$$\text{Acute: } \frac{\Delta H^+}{\Delta PaCO_2} = 0.8$$

$$\text{Chronic: } \frac{\Delta H^+}{\Delta PaCO_2} = 0.3$$

NEUROLOGIC CALCULATIONS

GLASGOW COMA SCALE (3–15)

= Eyes (1 − 4) + Motor (1 − 6) + Verbal (1 − 5)

Normal value: 15

TABLE A.1

SPECIFIC COMPONENTS OF THE GLASGOW COMA SCALE

Eye opening	
Spontaneous	4
To speech	3
To pain	2
Nil	1
Motor response	
Obeys commands	6
Localizes	5
Withdraws	4
Exhibits abnormal flexion	3
Exhibits abnormal extension	2
Nil	1
Verbal response	
Oriented	5
Confused, conversant	4
Uses inappropriate words	3
Uses incomprehensible sounds	2
Nil	1

CEREBRAL PERFUSION PRESSURE (mm Hg)

= $\overline{BP}$ − ICP

BODY SURFACE AREA FORMULA AND NOMOGRAM

BODY SURFACE AREA (BSA)

= (Height [cm])$^{0.718}$ × (Weight [kg])$^{0.427}$ × 74.49

See Figure A.1 for the nomogram for calculating BSA.

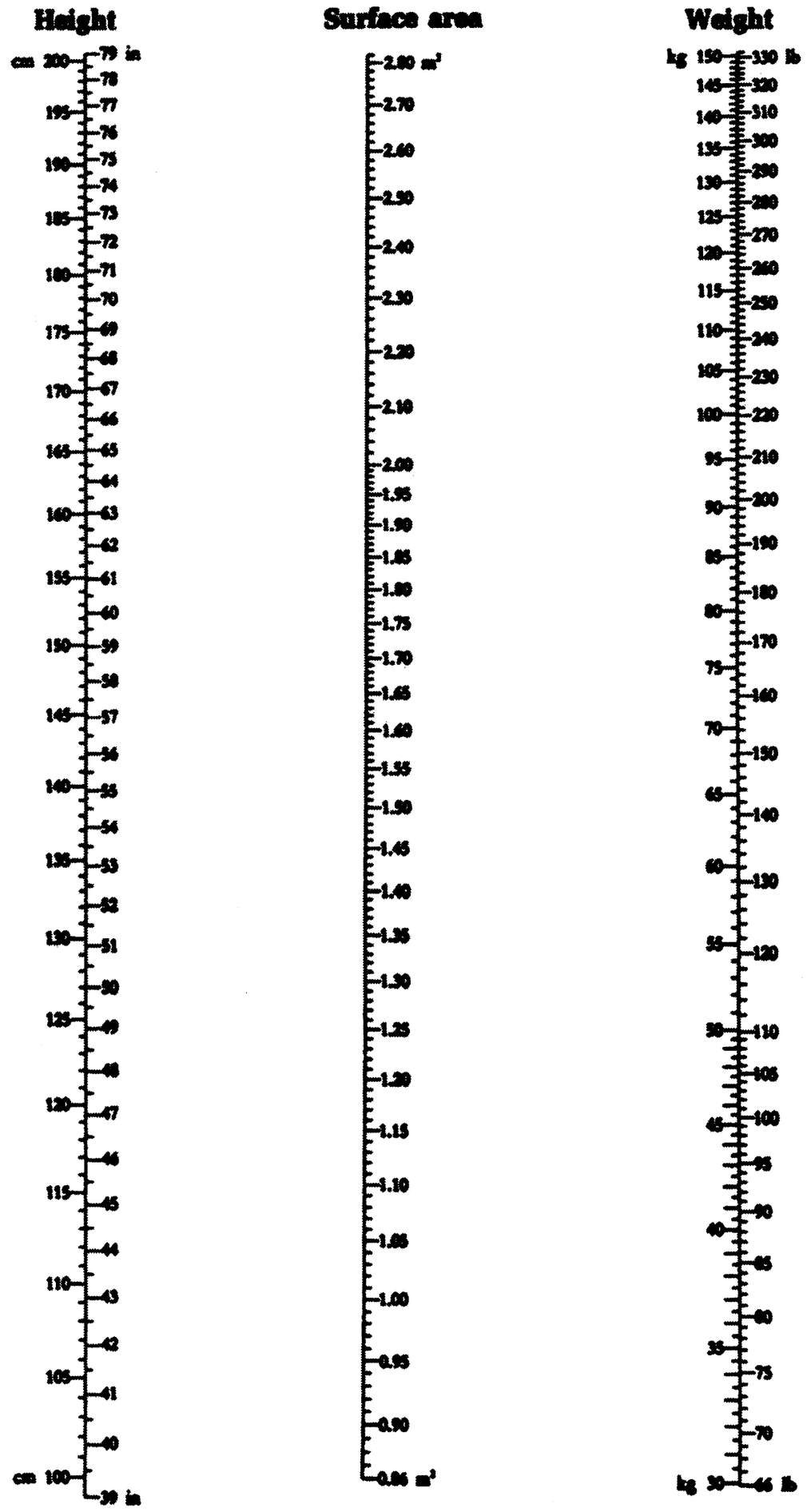

FIGURE A.1. Nomogram for calculation of body surface area (BSA) in square meters by height and weight.

PHARMACOLOGIC CALCULATIONS

DRUG CLEARANCE

= $V_d \times K_{el}$

DRUG HALF-LIFE

= $t_{1/2}$

$$= \frac{0.693}{K_{el}}$$

DRUG ELIMINATION CONSTANT

= K_{el}

$$= \frac{\ln\left(\frac{[\text{Peak}]}{[\text{Trough}]}\right)}{t_{peak} - t_{trough}}$$

DRUG LOADING DOSE

$$= V_d \times [\text{Target peak}]$$

DRUG DOSING INTERVAL

$$= \frac{-1}{K_{el}} \times \ln\left(\frac{\text{Desired trough}}{\text{Desired peak}}\right) + \text{Infusion time (hours)}$$

See ICU Acuity Scoring for the calculation of APACHE scores.

ICU ACUITY SCORING

SAPS II Score [1,2]

Type of admission		Points
	Scheduled surgery	0
	Unscheduled surgery	8
	Medical	6
Chronic diseases	None	0
	Metastatic carcinoma	9
	Hematologic malignancy	10
	AIDS	17
Age	< 40	0
	40–59	7
	60–69	12
	70–74	15
	75–79	16
	≥ 80	18
Temperature	< 39°C	0
	> 39°C	3
Heart rate	< 40	11
	40–69	2
	70–119	0
	120–159	4
	≥ 160	7
Systolic blood pressure	< 70 mm Hg	13
	70–99	5
	100–199	0
	≥ 200	2
Urine output	< 500 cc/24 h	11
	500–999 cc/24 h	4
	> 1,000 cc/24 h	0
Glasgow Coma Score	< 6	26
	6–8	13
	9–10	7
	11–13	5
	14–15	0
Serum urea or BUN	< 10	0
	10–29.9	6
	≥ 30	10
Serum sodium	> 146 mEq/L	1
	125–144 mEq/L	0
	< 125 mEq/L	5
Serum potassium	< 3 mEq/L	3
	3–4.9 mEq/L	0
	> 5 mEq/L	3
WBC	< 1,000/mm^3	12
	1,000–19,000/mm^3	0
	> 20,000/mm^3	3

(*continued*)

CONTINUED

Type of admission		Points
HCO_3^-	< 15 mEq/L	6
	15–19 mEq/L	3
	≥ 20	0
Bilirubin	< 4 mg/dL	0
	4–5.9 mg/dL	4
	≥ 6	9
PaO_2/FIO_2 (if ventilated or CPAP)	< 100	11
	100–199	9
	≥ 200	6

SAPS II, Simplified Acute Physiology Score II.

APACHE IV VARIABLES (NON-CABG PATIENTS) [3]

Age **Chronic Health Issues on Admission** *Use the one with the highest point value that is present* *Nonoperative and emergency surgery patients only* *otherwise = 0*	**Points**
AIDS	23
Hepatic failure	16
Lymphoma	13
Metastatic cancer	11
Leukemia/multiple myeloma	10
Immunosuppression	10
Cirrhosis	4
None/not available	0

Acute Physiology Score	
P_aO_2/FIO_2 ratio (or $P(A–a)O_2$ for intubated patients with $FIO_2 >= 0.5$	
Ventilated anytime during day 1	Y/N
ICU admission information	
Admit to ICU from floor	
Transfer to ICU from other hospital	
Admit to ICU from OR/PACU	
Emergency surgery	Y/N
Pre-ICU length of stay (# of days between ICU and hospital admission)	
Admitting diagnosis (see Diagnosis Tables)	
If DX is acute MI is the patient on thrombolytic therapy?	Y/N
Unable to obtain GCS (due to meds, anesthesia or sedation)	Y/N
GCS	

Acute Physiology Score (APS Score)

Pulse (beats/min) *Select heart rate furthest from 75*	
≤ 39	8
40–49	5
50–99	0
100–109	1
110–119	5
120–139	7
140–154	13
≥ 155	17

Mean blood pressure (MAP)
Select MAP furthest from 90

≤ 39	23
40–59	15
60–69	7
70–79	6
80–99	0
100–119	4
120–129	7
130–139	9
≥ 140	10

Temperature (degrees centigrade)
Select core temperature furthest from 38
Add 1 degree centigrade to axillary temps prior to selecting worst value

≤ 32.9	20
33–33.4	16
33.5–33.9	13
34–34.9	8
35–35.9	2
36–39.9	0
≥ 40	4

Respiratory rate (breaths/min)
Select respiratory rate furthest from 19
For patients on mechanical ventilation no points are given for respiratory rates of 6–12

≤ 5	17
6–11	8
12–13	7
14–24	0
25–34	6
35–39	9
40–49	11
≥ 50	18

PaO_2 (mm Hg)
Use only for nonintubated patients or intubated patients with FIO_2 < 0.5 (50%)

≤ 49	15
50–69	5
70–79	2
≥ 80	0

OR

A-aDO_2
Only use A-aDO_2 for intubated patients with FIO_2 ≥ 0.5 (50%)
Do not use PaO_2 weights for these patients

< 100	0
100–249	7
250–349	9
350–499	11
≤ 500	14

Hematocrit (%)
Select hematocrit furthest from 45.5

≤ 40.9	3
41–49	0
≥ 50	3

WBC (cu/mm)
Select WBC furthest from 11.5

< 1.0	19
1.0–2.9	5
3.0–19.9	0
20–24.9	1
≥ 25	5

Creatinine without ARF (mg/dL)
Select creatinine furthest from 1

≤ 0.4	3
0.5–1.4	0
1.5–1.94	4
≥ 1.95	7

OR

Creatinine with ARF (mg/dL)
Acute renal failure (ARF) is defined as creatinine ≥ 1.5 mg/dL as creatinine ≥ 1.5 mg/dL and urine output < 410 cc/d and no chronic dialysis

0–1.4	0
≥ 1.5	10

Urine Output (cc/day)
Total for day

≤ 399	15
400–599	8
600–899	7
900–1,499	5
1,500–1,999	4
2,000–3,999	0
≥ 4,000	1

BUN (mg/dL)
Select highest BUN

≤ 16.9	0
17–19	2
20–39	7
40–79	11
≥ 80	12

Sodium (mEq/L)
Select sodium furthest from 145.5

≤ 119	3
120–134	2
135–154	0
≥ 155	4

Albumin (g/dL)
Select albumin furthest from 3.5

≤ 1.9	11
2–2.4	6
2.5–4.4	0
≥ 4.5	4

Bilirubin (mg/dL)
Select highest bilirubin furthest from 0

≤ 1.9	0
2–2.9	5
3–4.9	6
5–7.9	8
≥ 8	16

Glucose (mg/dL)
Select glucose furthest from 130
Glucose ≤ 39 mg/dL is lower weight than 40–59

≤ 39	8
40–59	9
60–199	0
200–349	3
≥ 350	5

Neurological Abnormalities Score (see matrix)
Acid–Base Abnormalities Score (see matrix)

Adapted from Cerner Apache. *Apache IV Calculations.xls* with permission.
APACHE IV Score Calculator available at: http://www.cerner.com/public/filedownload.asp?LibraryID=40394. Accessed July 26, 2010.
Note: Mortality prediction calculations based on the APACHE IV are different for the day of ICU admission and subsequent days.

MPM0 III VARIABLES [4]

Category	Variable
Physiology	
	Coma or deep stupor at admission not due to drug overdose
	Heart rate > 150 beats/min
	Systolic blood pressure ≤ 90 mm Hg
Chronic diagnoses	
	Chronic renal compromise or insufficiency
	Cirrhosis
	Metastatic malignant neoplasm
Acute diagnoses	
	Acute renal failure
	Cardiac dysrhythmia
	Cerebrovascular accident
	Gastrointestinal bleeding
	Intracranial mass effect
Other variables	
	CPR within 24 hours prior to admission
	Mechanical ventilation within one hour of admission
	Medical or unscheduled surgery admission
	Full code status
	Age (years)

MPM_0-III variables are collected at the time of ICU admission or within 1 hour of admission.
Calculator available at: http://www.cerner.com/public/filedownload.asp?LibraryID=25783. Last accessed July 26, 2010.
Adapted from White Paper Report. Available at: http://www.cerner.com/public/filedownload.asp?LibraryID=34399. Accessed July 26, 2010.

TABLE A.2

APACHE IV NONOPERATIVE DIAGNOSES [3]

Diagnostic group
Cardiovascular diagnoses
- AMI
- Anterior
- Inferior/lateral
- Non-Q
- Other
- Cardiac arrest
- Cardiogenic shock
- Cardiomyopathy
- Congestive heart failure
- Chest pain, rule out AMI
- Hypertension
- Hypovolemia/dehydration (not shock)
- Hemorrhage (not related to GI bleeding)
- Aortic aneurysm
- Peripheral vascular disease
- Rhythm disturbance
- Sepsis (by infection site)
- Cutaneous
- Gastrointestinal
- Pulmonary

(*continued*)

TABLE A.2

CONTINUED

- Urinary tract
- Other location
- Unknown location
- Cardiac drug toxicity
- Unstable angina
- Cardiovascular, other

Respiratory diagnoses
- Airway obstruction
- Asthma
- Aspiration pneumonia
- Bacterial pneumonia
- Viral pneumonia
- Parasitic/fungal pneumonia
- COPD (emphysema/bronchitis)
- Pleural effusion
- Pulmonary edema (noncardiac)
- Pulmonary embolism
- Respiratory arrest
- Respiratory cancer (oral, larynx, lung, trachea)
- Restrictive lung disease (fibrosis, sarcoidosis)
- Respiratory disease, other

GI diagnoses
- GI bleeding, upper
- GI bleeding lower/diverticulitis
- GI bleeding, varices
- GI inflammatory disease
- Neoplasm
- Obstruction
- Perforation
- Vascular insufficiency
- Hepatic failure
- Intra/retroperitoneal hemorrhage
- Pancreatitis
- Gastrointestinal, other

Neurologic diagnoses
- Intracerebral hemorrhage
- Neurologic neoplasm
- Neurologic infection
- Neuromuscular disease
- Drug overdose
- Subdural/epidural hematoma
- Subarachnoid hemorrhage, intracranial aneurysm
- Seizures (no structural disease)
- Stroke
- Neurologic, other

Trauma diagnoses
- Trauma involving the head
- Head trauma with either chest, abdomen, pelvis, or spine injury
- Head trauma with extremity or facial trauma
- Head trauma only
- Head trauma with multiple other injuries
- Trauma, chest and spine trauma
- Trauma, spine only
- Multiple trauma (excluding head trauma)

Metabolic/endocrine diagnoses
- Acid–base, electrolyte disorder
- Diabetic ketoacidosis
- Hyperglycemic hyperosmolar nonketotic coma
- Metabolic/endocrine, other

Hematologic diagnoses
- Coagulopathy, neutropenia, thrombocytopenia, pancytopenia
- Hematologic, other

Genitourinary diagnoses
- Renal, other

Miscellaneous diagnoses
- General, other

TABLE A.3

APACHE IV SURGICAL DIAGNOSES [3]

Diagnostic group

Cardiovascular surgery
- Valvular heart surgery
- CABG with double or redo valve surgery
- CABG with single valve surgery
- Aortic aneurysm, elective repair
- Aortic aneurysm, rupture
- Aortic aneurysm, dissection
- Femoral–popliteal bypass graft
- Aortoiliac, aortofemoral bypass graft
- Peripheral ischemia (embolectomy, thrombectomy, dilation)
- Carotid endarterectomy
- Cardiovascular surgery, other

Respiratory surgery
- Thoracotomy, malignancy
- Neoplasm, mouth, larynx
- Thoracotomy, lung biopsy, pleural disease
- Thoracotomy, respiratory infection
- Respiratory surgery, other

GI surgery
- GI malignancy
- GI bleeding
- Fistula, abscess
- Cholecystitis, cholangitis
- GI inflammation
- GI obstruction
- GI perforation
- GI, vascular ischemia
- Liver transplant
- GI surgery, other

Neurologic surgery
- Craniotomy or transsphenoidal procedure for neoplasm
- Intracranial hemorrhage
- Subarachnoid hemorrhage (aneurysm, arteriovenous malformation)
- Subdural/epidural hematoma
- Laminectomy, fusion, spinal cord surgery
- Neurologic surgery, other

Trauma surgery
- Head trauma only
- Multiple trauma sites including the head
- Surgery for extremity trauma
- Multiple trauma (excluding the head)

Genitourinary surgery
- Renal/bladder/prostate neoplasm
- Renal transplant
- Hysterectomy
- Genitourinary surgery, other

Miscellaneous surgery
- Amputation (nontraumatic)

NORMAL VALUES OF EXPIRATORY PEAK FLOW [5]

There is a wide variability in peak expiratory flows due to individual differences. Values also vary slightly depending on the peak flow meter used.

TABLE A.4

NORMAL VALUES OF EXPIRATORY PEAK FLOW FOR MEN

	Height				
Age (y)	**60 Inches**	**65 Inches**	**70 Inches**	**75 Inches**	**80 Inches**
20	554	602	649	693	740
25	543	590	636	679	725
30	532	577	622	664	710
35	521	565	609	651	695
40	509	552	596	636	680
45	498	540	583	622	665
50	486	527	569	607	649
55	475	515	556	593	634
60	463	502	542	578	618
65	452	490	529	564	603
70	440	477	515	550	587

TABLE A.5

NORMAL VALUES OF EXPIRATORY PEAK FLOW FOR WOMEN

	Height				
Age (y)	55 Inches	60 Inches	65 Inches	70 Inches	75 Inches
20	390	423	460	496	529
25	385	418	454	490	523
30	380	413	448	483	516
35	375	408	442	476	509
40	370	402	436	470	502
45	365	397	430	464	495
50	360	391	424	457	488
55	355	386	418	451	482
60	350	380	412	445	475
65	345	375	406	439	468
70	340	369	400	432	461

From Higgins TL, Teres D, Copes WS, et al: Assessing contemporary intensive care unit outcome: An updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 35(3):827–835, 2007, with permission.

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5. Leiner GC, Abramowitz S, Small MJ, et al: Expiratory peak flow. Standards for normal subjects. Use as a clinical test of ventilatory function. *Am Rev Respir Dis* 86:644, 1963.

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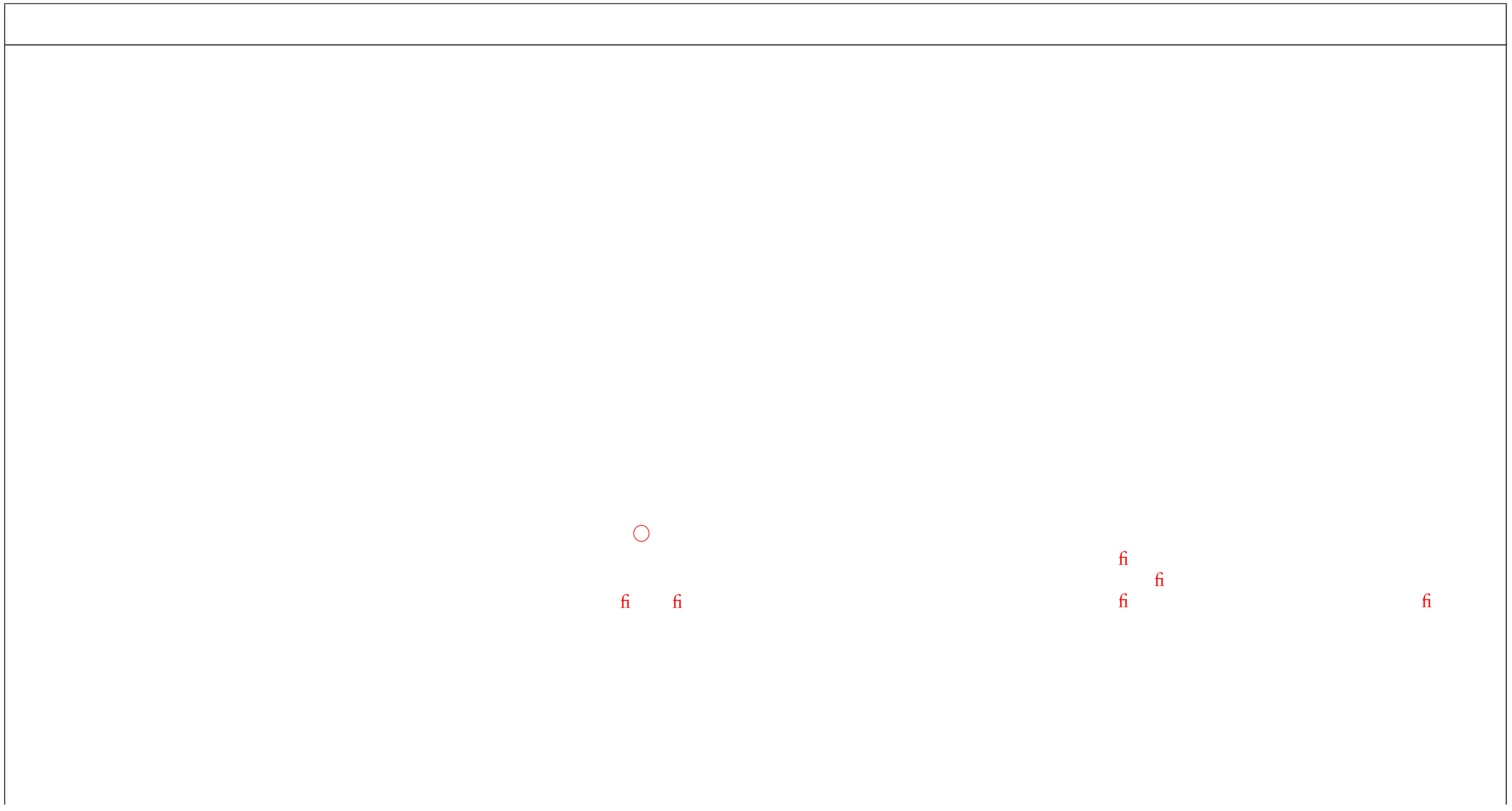

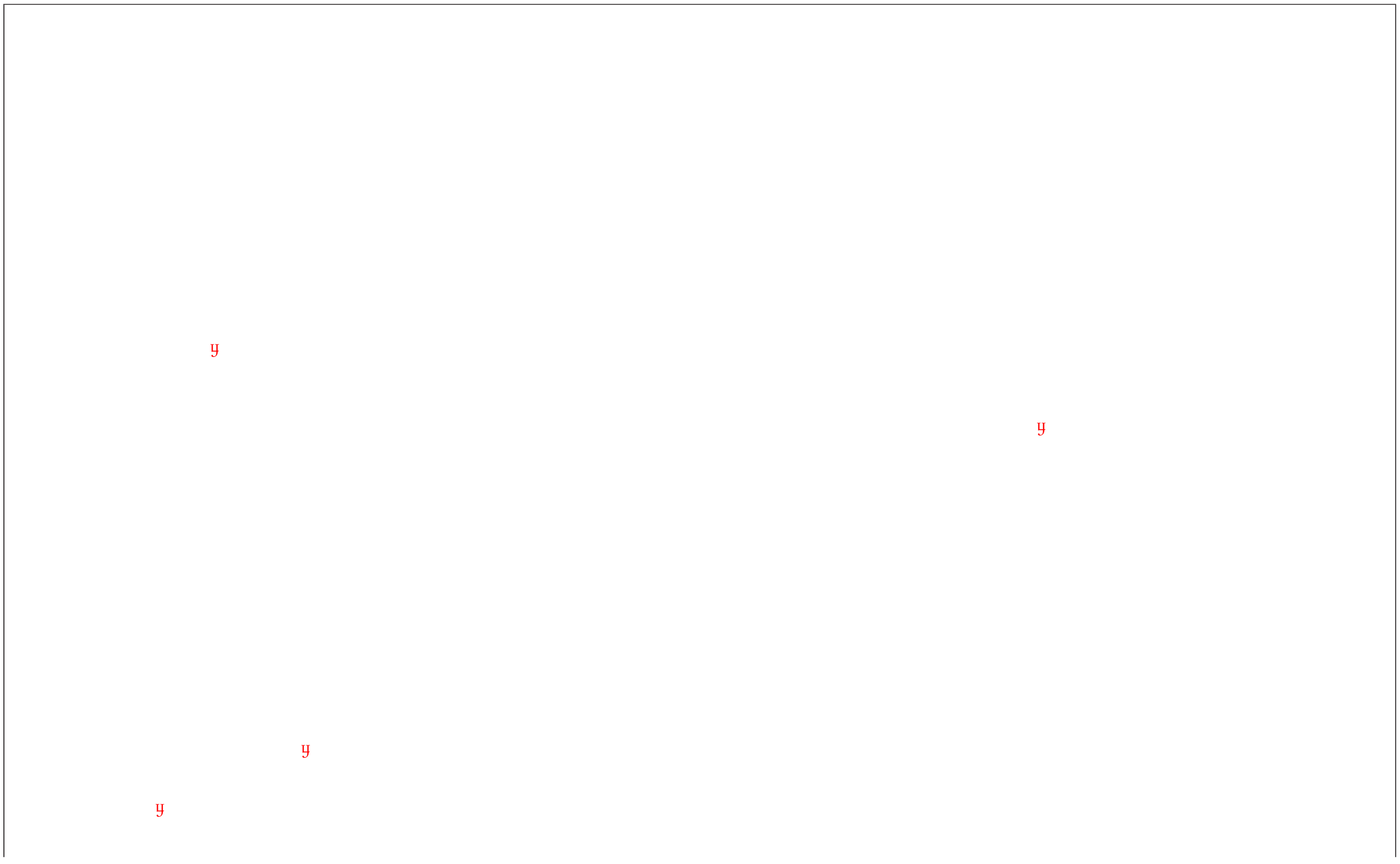


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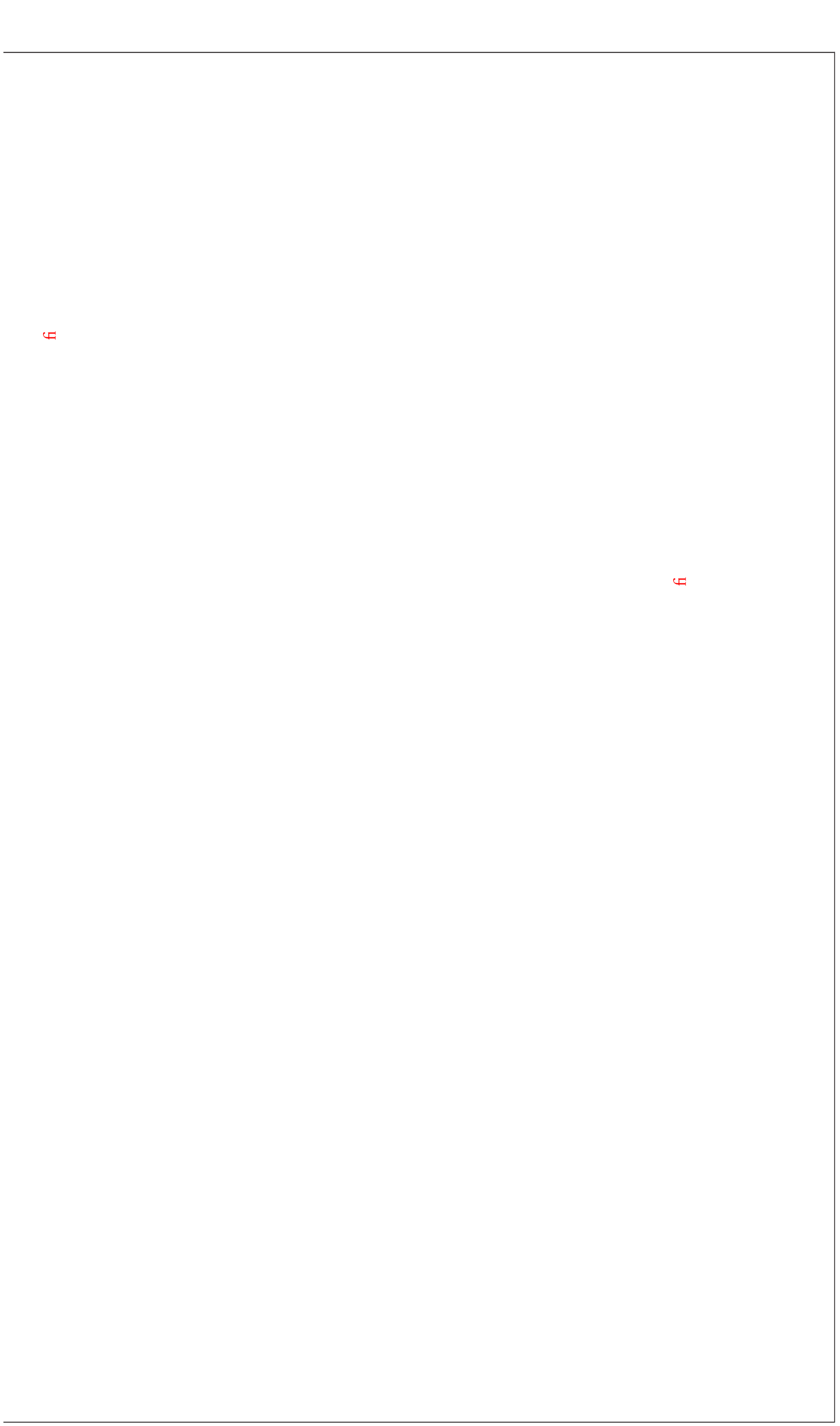

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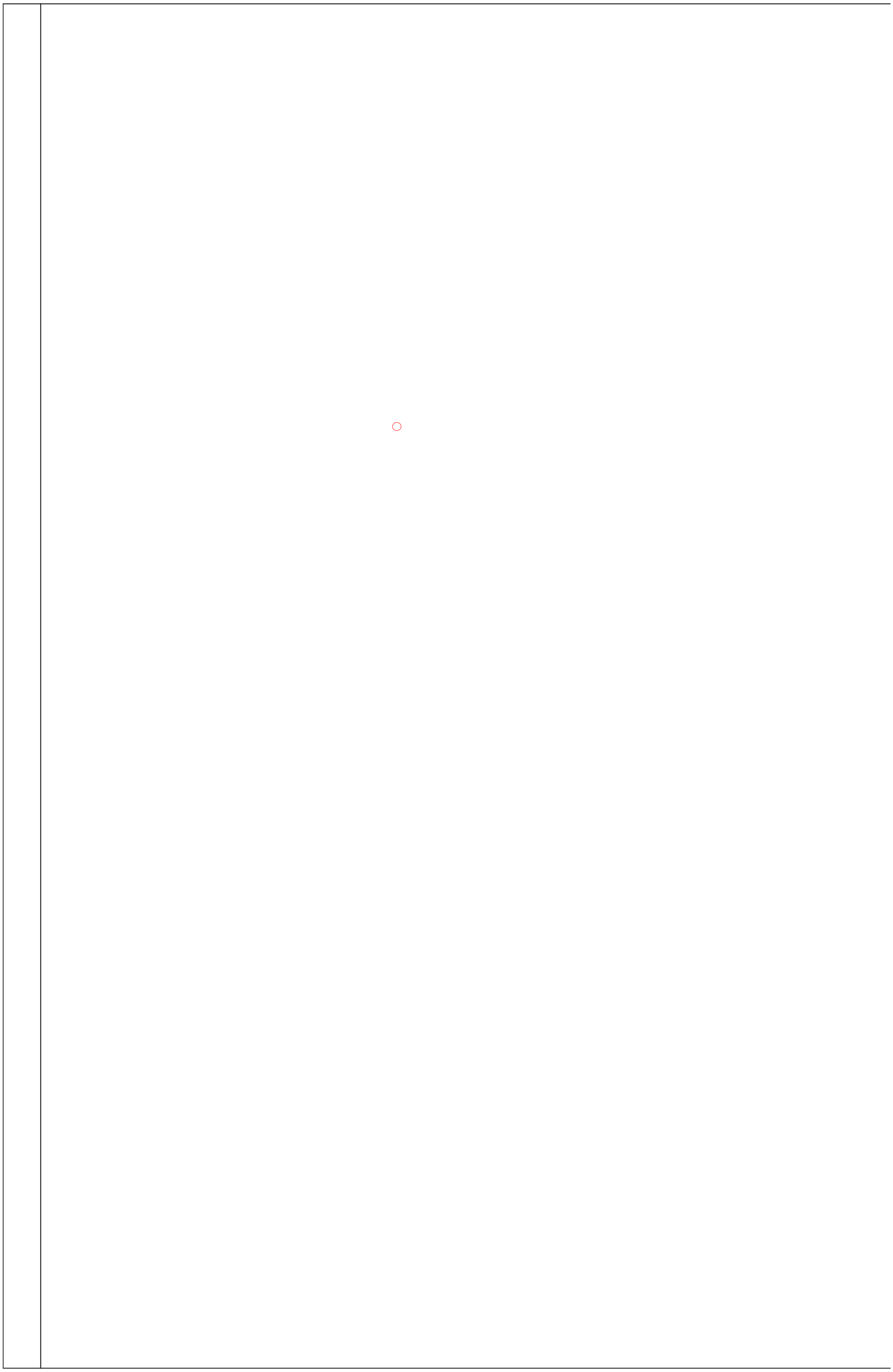

D50W = dextrose 50% water; D25W = dextrose 25% water; D10W = dextrose 10% water; h = hours; IM = intramuscular; IV = intravenous; LR = Lactated Ringer's; max = maximum; NS = normal saline; RaVR = terminal R wave in lead aVR; R/SaVR = R-wave/S-wave ratio in lead aVR; wks = weeks.

Box I. Digoxin antibody dosing calculator.

$$\text{Number of vials} = \frac{\text{Digoxin body burden to be neutralized in ng/mL (nmol/L} \times 1.28) \times \text{weight (kg)} \times \text{volume of distribution (Vd)}}{1{,}000 \times 0.6\ \text{mg/vial}}$$

V_d: Adults 8 L/kg

Box II. Polyethylene glycol solution (PEG) whole bowel irrigation.
Insert nasogastric/oral tube and administer PEG solution at 2 L/h for 5 h and clear rectal effluent is evident; doubtful patients would be cooperative or tolerate oral PEG.

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Note: Page numbers followed by *f* and *t* indicates figure and table respectively.